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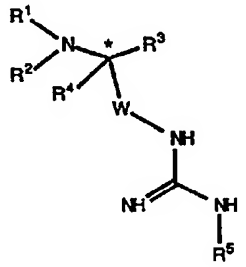
(54) Title: GUANIDINE COMPOUNDS AS REGULATORS OF NITRIC OXIDE SYNTHASE



(I)

(57) Abstract

Guanidine compounds of formula (I) or a pharmaceutically-acceptable salt, ester, amide or prodrug thereof, which are regulators of nitric oxyde synthase and are useful in the treatment of disorders of the vascular system including hypotension, hypertension, shock, atherosclerosis, migraine, or ischemia; disorders of the gastrointestinal system including reflux esophogitis, diarrhea, or irritable bowel syndrome; disorders of bronchial smooth muscles including asthma; and inhibition of blood platelet aggregation during angioplasty or preservation and processing of platelets for transfusions and perfusions, and diabetes.

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GUANIDINE COMPOUNDS AS REGULATORS OF NITRIC OXIDE SYNTHASE

CROSS REFERENCE TO OTHER RELATED APPLICATIONS

This Application is a continuation-in-part of copending allowed U.S. Patent Application Serial Number 07/755,398, filed September 5, 1991, which is a continuation-in-part of U.S. Patent Application Serial Number 07/369,364, filed June 21, 1989, now abandoned.

TECHNICAL FIELD

The present invention relates to novel unsaturated guanidino compounds, to compositions thereof useful in regulating the production of soluble guanylate cyclase or nitric oxide, to intermediates useful in the production thereof, and to a method of treating disorders of the vascular system or diseases of the cartilage, including hypotension, hypertension, coronary vasospasm, cerebral vasoconstriction, cardiomyopathy, atherogenesis, atherosclerosis, myocardial ischemia, cerebral ischemia, diabetes, endotoxemia, sepsis, asthma and rhinitis, synovitis, chondroarthritis and osteoarthritis.

BACKGROUND OF THE INVENTION

Furchgott (*Nature*, **1980**, 288:373-6) reported in 1980 that endothelial cells release a powerful vasodilator which is termed endothelium-derived relaxing factor (EDRF). Subsequent research has shown that many endothelium-dependent receptor agonists, including, for example, adenosine diphosphate (ADP), adenosine triphosphate (ATP), 5-hydroxytryptamine (5-HT), thrombin, acetylcholine (ACh), vasoactive intestinal polypeptide (VIP), oxytocin, cholecystokinin (CCK), calcitonin gene-related peptide, noradrenaline, histamine, calcium ionophores, melittin and ergometrine invoke the release of EDRF. The release of EDRF, in turn, stimulates the soluble form of the enzyme guanylate cyclase, thereby increasing levels of the second messenger, cyclic guanosine monophosphate (cGMP), which, in turn, produces vasorelaxation. Reviews are available which discuss this process in more detail (see, for example, J.F. Kerwin, *Med. Res. Rev.*, **1994**, 14:23-74; A.M. Katz, *J. Am. Coll. Cardiol.*, **1988**, 12:797-806; J.A. Angus and T.M. Cocks, *Pharmaceutical Therapeutics*, **1989**, 41:303-52; S.A. Waldman and F. Murad, *Pharmacological Reviews*, **1987**, 39:163-196; F. Murad, *J. Clin. Invest.*, **1986**, 78:1-5; L.J. Ignarro, *Biochem. Pharmacol.*, **1991**, 41:485-90; and S. Moncada, R.M.J. Palmer and E.A. Higgs, *Pharmacological Reviews*, **1991**, 43:109-142).

Pharmacological characterization of EDRF and its effects has been an active area of research over the past eleven years (K. Shikano *et al.*, *J. Pharmacol. Exp. Therap.*, **1988**, 247: 873-81 and L.J. Ignarro, *Annu. Rev. Pharmacol. Toxicol.*, **1990**, 30: 535-60), and now there is substantial evidence that nitric oxide (NO) is the major endothelium-derived relaxing factor (R.M.J. Palmer *et al.*, *Nature*, **1987**, 327: 524-6; S. Moncada *et al.*, *Biochem. Pharmacol.*, **1989**, 38: 1709-15; and S. Moncada *et al.*, *Hypertension*, **1989**, 12: 365-72). In particular, nitric oxide (NO) was tested and found to elicit a potent and transient relaxation of bovine coronary artery accompanied by cGMP accumulation (C.A. Guetter *et al.*, *J. Cyclic Nucleotide Res.*, **1979**, 5: 211-24) and it was also shown to activate soluble guanylate cyclase and to elevate tissue cGMP levels.

Recent reports (H.H.H.W. Schmidt *et al.*, *European J. Pharmacol.*, **1988**, 154: 213-6 and S. Moncada *et al.*, *Hypertension*, **1988**, 12: 365-72) have suggested that L-arginine may be the endogenous source of EDRF (NO), and this hypothesis is further supported by the observation that EDRF (NO) production is inhibited by the simple arginine derivative, N^G-methylarginine (R.M.J. Palmer *et al.*, *Biochem. Biophys. Res. Comm.*, **1988**, 153: 1251-56; S. Moncada *et al.*, *Biochemical Pharmacology*, **1988**, 37: 2495-2501; and I. Sakuma *et al.*, *Proc. Natl. Acad. Sci. USA*, **1988**, 85: 8664-7).

Increasing evidence has been uncovered that suggests EDRF or EDRF-like substances may also control cGMP production in non-endothelial cells (J. Garthwaite, *Nature*, **1988**, 336: 385-388 and T.J. Rimele *et al.*, *J. Pharmacol. Exp. Therap.*, **1988**, 245: 102-111) and that this method of guanylate cyclase regulation may be ubiquitous. A role in the regulation of neural transmission and a role in the neural control of gastrointestinal smooth muscle function has been elucidated (J. Collier and P. Vallance, *Trends in Pharmacological Sciences*, **1989**: 428-31 and K.M. Desai *et al.*, *Nature*, **1991**, 351: 477-9). Compounds that control, inhibit, or otherwise regulate this pathway, therefore, have potentially many and varied therapeutic applications, for instance, as analgesics (Duarte *et al.*, *European J. Pharmacology*, **1990**, 186: 289-93), as cerebroprotectives (cf. Southham *et al.*, *J.Neurochem.*, **1991**, 56: 2072-81) and as hypocholesteremics (Cooke *et al.*, *Circulation*, **1991**, 83: 1057-62).

Recent work has shown that there are many isoforms of the EDRF (NO) synthase enzyme. The primary distinction among these isoforms is whether they are constitutive or inducible forms, but other factors which serve to distinguish these isoforms are their cellular localization and their cofactor requirements. Many of these isoforms have been arbitrarily given Roman numeral designations

and are described in the table below, wherein NADPH represents reduced nicotinamide adenine dinucleotide phosphate, BH_4 represents tetrahydrobiopterin, FAD represents flavin adenine dinucleotide and FMN represents flavin mononucleotide.

Type	Cosubstrates & Cofactors	Regulated by	M_r of denatured protein*	Present in
I (soluble)	NADPH, BH_4	Ca^{++}, calmodulin	160 kDa**	brain and cerebellum
II (soluble)	NADPH, BH_4, FAD/FMN, thiols, Mg^{++}	induced by endotoxin and cytokines	135 kDa**	macrophages
III (particulate)	NADPH BH_4	Ca^{++}, calmodulin	130 kDa**	endothelial cells

* Molecular weight determination by sodium dodecyl sulfate/polyacrylamide gel electrophoresis

** kiloDaltons

Isoform I has been purified and characterized by Bredt and Snyder (*Proc. Natl. Acad. Sci. USA*, **1989**, 87: 682-685) and by Schmidt *et al.* (*Proc. Natl. Acad. Sci. USA*, **1989**, 88: 365-369). Isoform II has been purified and characterized by Kawai *et al.* (*J. Biological Chemistry*, **1991**, 266: 12544-47). Isoform III has been purified and characterized by Pollock *et al.* (*Proc. Natl. Acad. Sci. USA*, **1991**, 88: 10480-4). Isoform-specific agents may offer the advantage of selectivity, i.e., desired therapeutic effect with fewer or more tolerable side-effects.

Compounds which act directly to regulate NO synthesis or in an indirect fashion to regulate the production of cGMP through regulation of the effect of endogenous EDRF (NO) on soluble guanylate cyclase are useful in the treatment of those disease states associated with smooth muscle and smooth muscle tone, especially those involving airway, gastrointestinal and vascular muscle, and platelet function.

Support can be found within the scientific and medical literature for a broad range of uses of such compounds. For example hypotension (S. Moncada, *Acta Physiologica Scandinavica*, **1992**, 145: 201-227), endotoxemia, shock, and sepsis (T. Evans *et al.*, *Circulatory Shock*, **1993**, 41: 77-81; S. M. Hollenberg *et al.*, *Am J. Physiol.*, **1993**, 264: H660-3; Y. A. Shi *et al.*, *J. Pediatrics*. **1993**, 123: 435-438), hypertension (S. H. Abman *et al.*, *Pediatrics*,

1993, 92: 606-609; K. G. Allman et al., *Archives of Disease in Childhood*, 1993, 69: 449-450; S. L. Archer et al., *Circulation*, 1993: 285-285), and cerebral vasoconstriction and vasodilation (K. Alving et al, *Acta Physiol. Scandinavica*, 1992, 146: 407-408; S. Amerini *et al.*, *Pharmacological Research*, 1992, 25: 103-104; I. P. Brown *et al.*, *FASEB Journal*, 1992, 6: A1750-A1750), such as migraine (J. Olesen *et al.*, *NeuroReport*, 1993, 4: 1027-1030), ischemia (J. S. Beckman, *J. Dev. Physiol.*, 1991, 15: 53-9; G. J. Lees, *J. Neurol. Sci.*, 1993, 114: 119-22; A. Buisson et al., *J. Neurochemistry*, 1993, 61: 690-696; J. P. Nowicki *et al.*, *Eur. J. Pharmacology*, 1991, 204: 339-40), thrombosis (X. L. Ma *et al.*, *Circulation Research*, 1993, 72: 403-412; M. Ovize *et al.*, *J. Cardiovascular Pharmacol.*, 1990, 16: 641-5; M. R. Siegfried *et al.*, *J. Pharmacol. Exp. Therap.*, 1992, 260: 668-75; A. M. Lefer *et al.*, *Annual Rev. Pharmacol. Toxicol.*, 1993, 33: 71-90), and platelet aggregation, including preservation and processing of platelets for transfusions and perfusion technologies (R. Bowen *et al.*, *J.Cardiovascular Pharmacol.*, 1991, 17: 424-33; R. C. Ashmore *et al.*, *Biochem. Biophys. Res. Comm.*, 1990, 166: 909-15; J. Albina*et al.*, *J. Surg. Res.*, 1991, 50: 403-9; P. Mannaioni *et al.*, *Agents and Actions Supplement*, 1991, 33: 423-8). Additional examples include atherosclerosis (F. V. DeFeudis, *Life Sciences*, 1991, 49: 689-705; A. M.Lefer *et al.*, Pharmacol. Res., 1991, 23: 1-12; P. M. Vanhoutte, *Eur. Heart J.*, 1991, 12: 25-32), diseases of the bronchial passages, such as asthma (J. E. Albina *et al.*, *J. Immunol.*, 1989, 143: 3641-6; E. E. Daniel *et al.*, *Am. Rev. Respir. Dis.*, 1991, 143:S3-5; A. Ialenti*et al.*, *Eur. J. Pharmacol.*, 1992, 211: 177-182; R. G. Knowles *et al.*, *Biochem.* Biophysi. *Res. Comm.*, 1990, 172: 1042-8), rhinitis, diseases of the optic musculature, diseases of the gastrointestinal system, such as reflux esophagitis (GERD), spasm, diarrhea, irritable bowel syndrome, and other gastrointestinal motile dysfunctions (A. T. Dinh Xuan *et al.*, *Brit. J. Pharmacol.*, 1990, 99: 9-10; N. K. Boughton-Smith *et al.*, *Agents And Actions*, 1992, NSI: C3-C9; J. L. Conklin *et al.*, *Gastroenterology* 1993, 104: 1439-44; K. M. Desai *et al.*, *Nature*, 1991, 351: 477-9; K. Endoh *et al.*, *Gastroenterology*, 1993, 104: 114-21; Y. F. Li *et al.*, *Gastroenterology*, 1992, 103: 1392-1392; M. Miller *et al.*, *Scand. J. Gastroenterol.*, 1993, 28: 149-154; M. Stark *et al.*, *Gastroenterology*, 1993, 104: 398-409; S. Yamato *et al.*, *Gastroenterology* 1992, 103: 197-204; T. Yamada *et al.*, *Gastroenterology*, 1993, 104: 759-71).

Examples of known compounds that act to regulate the production of cGMP by this method may be grouped into four categories: (1) those compounds, for example, methylene blue, which directly or indirectly (through superoxide anion) oxidize EDRF (NO) and thereby inactivate it (R.J. Gryglewski *et al.*, *Nature*, 1986, 320: 454-6 and S. Moncada *et al.*, *Proc. Natl. Acad. Sci.*

USA, **1986**, 83: 9164-68); (2) those agents, for example, hemoglobin, which directly bind either EDRF (NO) itself or one of its end products; (3) those agents which remove superoxide anion $(O_2)^-$ and other oxidants, thereby enhancing the effect of EDRF (for example, the enzyme superoxide dismutase removes superoxide anion by converting it to molecular oxygen (O_2) and hydrogen peroxide); and (4) the nitrovasodilators, such as nitroglycerin, which provide nitrogen oxide to stimulate guanylate cyclase (F. Murad, *J. Clin. Invest.*, **1986**, 78: 1-5). With the exception of the nitrovasodilators, none of these categories of compounds has provided a viable therapeutic agent for the regulation of cGMP production in disease states. The nitrovasodilators, because they provide nitrogenous oxides indiscriminately to numerous target tissues, and thus lead to such complications as tolerance (A. Mulsch *et al.*, *European J. Pharmacol.*, **1988**, 158: 191-8), may not be the ultimate therapeutic agents of choice. More recently it has been reported that N-hydroxyarginine is a substrate for the NO synthase enzyme (Steuhr *et al.*, *J. Biol. Chem.*, **1991**, 266: 6259).

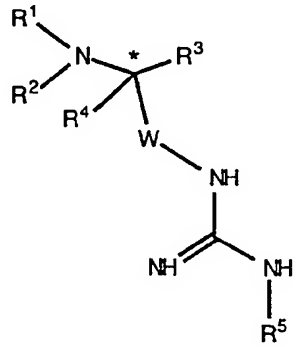
Compounds somewhat similar to those of the present invention include N^G-acyl derivatives and N^G-alkyl derivatives of arginine for use in oral hygiene compositions, which were disclosed in Silbering *et al.*, U.S. Patents 4,499,067 and 4,499,068, issued February 12, 1985, and cytoprotective guanidine derivatives useful in ischemic diseases, which were disclosed in Sportletti *et al.*, U.S. Patent 4,789,681, issued December 6, 1988.

Japanese Patent Application J67008012, published March 31, 1967, disclosed a method for production of α-amino, ω-guanidinocarboxylic acids, and Japanese Patent Application J55022601, published February 18, 1980, disclosed α-protected aminoarginine esters that are useful in enzymatic activity determinations. Finally, Japanese Patent Application J51075023, published June 29, 1976, disclosed the preparation of N^G-alkyl arginines and Japanese Patent Application J72042823, published October 28, 1972, disclosed a method for the preparation of N-acetyl-γ-hydroxyarginine.

Further, Harmon *et al.*, in U.S.Patent 2,929,845, issued March 22, 1960, disclosed a guanidino amino alcohol as an antifungal compound; Christiansen, in *Peptides, Proc. Eur. Prot. Soc.*, 1980: 612-6, described another guanidino amino alcohol as an intermediate in synthesis of bradykinin analogs; and Ajito *et al.*, in *Pharm. Res. Lab.*, 1988; 27, disclosed yet other guanidino amino alcohols; but none of these references disclose or suggest the novel compounds of the present invention.

SUMMARY OF THE INVENTION

The present invention is directed to regulators of nitric oxide synthase that indirectly modulate cyclic guanosine monophosphate (cGMP) production which have the formula:



(I)

or a pharmaceutically-acceptable salt, ester, amide or prodrug thereof.

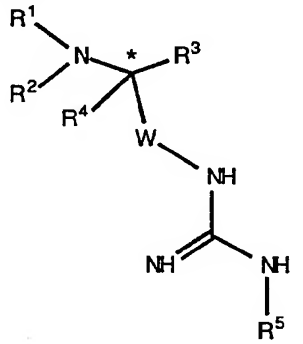
The present invention is also directed to pharmaceutical compositions comprising a therapeutically-effective amount of a compound of formula (I) and a pharmaceutically-acceptable carrier or diluent, and to a method of treating disorders of vascular smooth muscles, macrophages, neurons, platelets, bronchial smooth muscles, optic muscles and gastrointestinal smooth muscles in humans and mammals, in addition to sickle cell anemia and diabetes, by administration of a compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel unsaturated guanidino compounds and pharmaceutical compositions thereof which regulate nitric oxide synthase and thereby indirectly modulate levels of cyclic guanosine monophosphate. These compounds may, therefore, be used in the treatment of disorders of vascular smooth musculature, macrophages or neurons, such as hypotension, endotoxemia, sepsis, hypertension, shock, cerebral vasoconstriction, cerebral vasodilation, or non-migraine headache; in disease states involving platelet aggregation, including preparation of platelets for transfusion or perfusion; in angioplasty, ischemia, thrombosis, coronary vasospasm, cardiomyopathy, atherogenesis, atherosclerosis, sickle cell anemia and diabetes; in diseases involving the bronchial passages such as asthma; in diseases of the optic

musculature; and in disorders of the gastrointestinal system, such as diarrhea, irritable bowel syndrome, spasm, and reflux esophagitis (GERD).

In particular, the invention is directed to compounds of formula (I):



(I)

or a pharmaceutically-acceptable salt, ester, amide or prodrug thereof, wherein

* represents a potential chiral center;

R^1 is selected from the group consisting of:

(1) hydrogen;
(2) C_1-C_6-alkyl;
(3) C_6-C_{12}-aryl-C_1-C_4-alkyl, as defined below;
(4) substituted C_6-C_{12}-aryl-C_1-C_4-alkyl, as defined below;
(5) N-protecting group, as defined below;
(6) -CO-C_1-C_6-alkyl, wherein CO, here and below, represents carbonyl;
(7) -CO-C_6-C_{12}-aryl, wherein C_6-C_{12}-aryl is as defined below;
(8) -CO-substituted C_6-C_{12}-aryl, wherein substituted C_6-C_{12}-aryl is as defined below;
(9) -CO-(C_6-C_{12}-aryl-C_1-C_4-alkyl); and
(10) -CO-(substituted C_6-C_{12}-aryl-C_1-C_4-alkyl);

R^2 is selected from the group consisting of:

(1) hydrogen;
(2) C_1-C_6-alkyl;
(3) C_6-C_{12}-aryl-C_1-C_4-alkyl; and
(4) substituted C_6-C_{12}-aryl-C_1-C_4-alkyl;

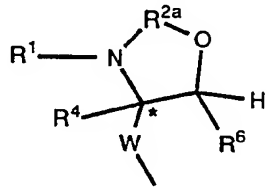
R^3 is selected from the group consisting of:

(1) CH(OH)-R^6, wherein R^6 is hydrogen, C_1-C_6-alkyl, or C_6-C_{12}-aryl; and
(2) CH(OR^7)-R^6, wherein R^6 is as defined above, and R^7 is

C_1-C_6-alkyl or a hydroxy-protecting group, as defined below;

or

R^2 and R^3 are linked together by a single bond to form a nitrogen-containing ring of the formula:



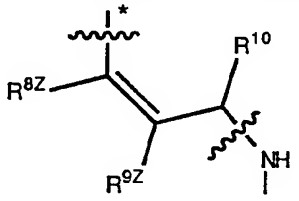
wherein R^1 and R^6 are as defined above, R^4 and W are as defined below, and R^{2a} is $-CR^{13}R^{14}$, wherein R^{13} is selected from the group consisting of:

(1) hydrogen;
(2) C_1-C_6-alkyl;
(3) substituted C_1-C_6-alkyl, as defined below;
(4) C_6-C_{12}-aryl;
(5) substituted C_6-C_{12}-aryl;
(6) C_2-C_6-alkenyl;
(7) carboxy;
(8) C_1-C_4-alkoxycarbonyl, as defined below;
(9) carboxamido; and
(10) cyano; and

R^{14} is hydrogen or C_1-C_6-alkyl;

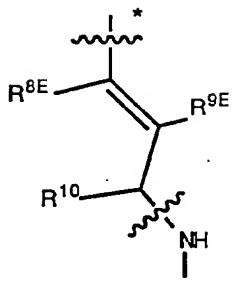
R^4 is hydrogen or C_1-C_4-alkyl;

W is selected from the group consisting of:



1)

wherein the wavy lines identify the bonds which connect to the appropriate atoms of (I), and R^{8Z} is hydrogen or C_1-C_4-alkyl, R^{9Z} is hydrogen, C_1-C_4-alkyl or halogen, and R^{10} is hydrogen or methyl; and



(2)

wherein R^{8E} is hydrogen or C_1-C_4-alkyl, R^{9E} is selected from the group consisting of:

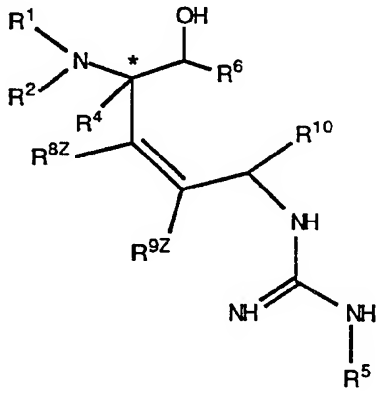
(1) hydrogen;
(2) C_1-C_4-alkyl;
(3) C_6-C_{12}-aryl-C_1-C_6-alkyl;
(4) substituted C_6-C_{12}-aryl-C_1-C_6-alkyl;
(5) halo-C_1-C_2-alkyl, as defined below; and
(6) halogen; and

R^{10} is hydrogen or methyl; and

R^5 is selected from the group consisting of:

(1) hydrogen;
(2) C_1-C_3-alkyl;
(3) cyano;
(4) nitro;
(5) hydroxy;
(6) amino;
(7) $-OR^{11}$, wherein R^{11} is a hydroxy-protecting group; and
(8) $-NHR^{12}$, wherein R^{12} is an N-protecting group;

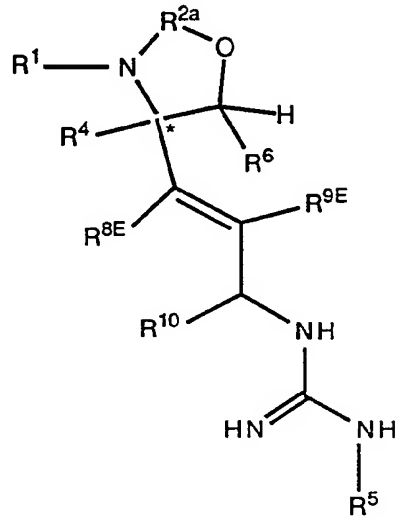
In one embodiment of the present invention are compounds represented by formula (Ia):



, (1a),

wherein R^1, R^2, R^4, R^5, R^6, R^{8Z}, $R^{9Z}$and R^{10} are as defined above. A preferred embodiment is the compound (1a), wherein R^1, R^2, R^4, R^6, R^{8Z}, $R^{9Z}$and R^{10} are hydrogen and R^5 is nitro.

In another embodiment of the invention are compounds represented by the formula (1b):



, (1b),

wherein R^1, R^{2a}, R^4, R^5, R^6, R^{8E}, R^{9E} and R^{10} are as defined above. A preferred embodiment is the compound (1b) wherein R^5 and R^6 are hydrogen and the chiral center is S.

When a variable or substituent occurs more than once in any structure, it is understood to be independently selected at each occurrence.

Representative of the compounds of the invention are:

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-nitroguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Nitroguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

1-Guanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-aminoguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Aminoguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-hydroxyguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Hydroxyguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-methylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-ethylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Ethylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

N^4-Boc-N^G-nitroguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Nitroguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^4-Boc-N^G-methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(R)-4-(3-N^G-methylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Methylguanidinyl-4(R)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Guanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(R)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

1-Guanidinyl-4(R)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidino-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Guanidinyl-4(S)-amino-2-benzyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-methylguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Methylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-propylguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Propylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-nitroguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Nitroguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol;

N^4-t-Butyloxycarbonyl-4-amino-1-N^G-nitroguanidino-5-methoxy-(4,S)-2,Z-pentene;

4-Amino-1-N^G-nitroguanidino-5-methoxy-(4,S)-2,Z-pentene hydrochloride;

N^2-Methyl-N^2-t-butyloxycarbonyl-2,5-diamino-1-t-butyldimethylsilyloxy-(2,S)-3,Z-pentene;
N^4-Methyl-4-amino-1-(N^G-nitroguanidino)-(4,S)-2,Z-penten-5-ol;
3-(1,1-Dimethylethyl)-(R)-4-(3-N^G-nitroguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;
N^G-Nitroguanidinyl-4(R)-amino-pent-2,Z-ene-5-ol;
N^G-Aminoguanidino-4(S)-amino-pent-2,Z-ene-5-ol;
3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-methylguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;
N^G-Methylguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol;
2-(N^G-Nitroguanidino)-5-aminohex-3,Z-en-6-ol;
2-(N^G-Nitroguanidino)-5-aminohex-3,Z-en-6-ol;
3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-benzylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate; and
N^G-Benzylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol.

Illustrative of the preferred compounds of the invention are:
N^G-Nitroguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
3-(1,1-Dimethylethyl)-(S)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;
N^G-Aminoguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
N^G-Methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
N^G-Ethylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
N^G-Nitroguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;
N^G-Methylguanidinyl-4(R)-amino-pent-2,E-ene-5-ol;
N^G-Guanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;
3-(1,1-Dimethylethyl)-(R)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;
N^G-Guanidinyl-4(S)-amino-2-benzyl-pent-2,E-ene-5-ol;
N^G-Methylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;
N^G-Nitroguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol;
4-Amino-1-N^G-nitroguanidino-5-methoxy-(4,S)-2,Z-pentene hydrochloride;
N^4-Methyl-4-amino-1-(N^G-nitroguanidino)-(4,S)-2,Z-penten-5-ol;
N^G-Nitroguanidinyl-4(R)-amino-pent-2,Z-ene-5-ol;
N^G-Aminoguanidino-4(S)-amino-pent-2,Z-ene-5-ol; and
N^G-Methylguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol.

Illustrative of the most preferred compounds of the invention are:

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Aminoguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

N^G-Methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

N^G-Ethylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

N^G-Nitroguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

N^G-Guanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(R)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Methylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

N^G-Nitroguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol; and

N^G-Aminoguanidino-4(S)-amino-pent-2,Z-ene-5-ol.

Throughout the Specification and Claims:

"C_2-C_6-Alkenyl" refers to a straight-or branched-chain radical from 2-to-6 carbon atoms, which contains at least one carbon-carbon double bond.

"C_1-C_4-alkoxy or C_1-C_6-alkoxy", refers to the specified alkyl group, as defined below, attached to a linking oxygen atom.

"C_1-C_4-alkoxycarbonyl" refers to a C_1-C_4-alkoxy group attached to a linking carbonyl group, and includes, for example, methoxycarbonyl, ethoxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, isobutyloxycarbonyl and t-butyloxycarbonyl.

"Alkyl" refers to straight- or branched-chain alkyl radicals containing from 1-to-3 carbon atoms ("C_1-C_3-alkyl"), 1-to-4 carbon atoms ("C_1-C_4-alkyl") or from 1-to-6 carbon atoms (C_1-C_6-alkyl) including, but not limited, to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 2,2-dimethylbutyl, n-hexyl, and the like.

"C_6-C_{12}-Aryl" or "C_6-C_{12}-aryl group", as used herein, refers to carbocyclic aromatic isolated or fused rings of a total of from 6-to-12 carbon atoms, for example, phenyl, naphthyl, indanyl, fluorenyl, terahydronaphthyl, indenyl, or isoindenyl.

"C_6-C_{12}-Aryl-C_1-C_4-alkyl" refers to a C_6-C_{12}-aryl group, as defined above, appended to a C_1-C_4-alkyl radical, as defined above, including, but not limited to, benzyl, phenylethyl, naphthylmethyl, and the like.

"C_6-C_{12}-Aryloxy" refers to $R^{22}O$-, wherein R^{22} is a C_6-C_{12}-aryl group, as defined above.

"Halogen" refers to fluoro (F), chloro (Cl), bromo (Br) or iodo (I).

"Halo-C_1-C_2-alkyl" refers to a C_1-C_4-alkyl radical, as defined above, in which one-to-three hydrogen atoms have been replaced by a halogen, including, but not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, and the like.

"Hydroxy-protecting group" or "O-protecting group" refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures and includes, but is not limited to, substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)-ethoxymethyl, benzyl, and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl and t-butyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; cyclic acetals and ketals, for example, methylene acetal, acetonide and benzylidene acetal; cyclic ortho esters, for example, methoxymethylene; cyclic carbonates; and cyclic boronates.

"N-Protecting group", "nitrogen-protecting group" or "N-protected" refers to those groups intended to protect an amino group or the N-terminus of an amino acid or peptide against undesirable reactions during synthetic procedures or to prevent the attack of exopeptidases on the compounds or to increase the solubility of the compounds, and includes, but is not limited to, sulfonyl; acyl, such as acetyl, pivaloyl and benzoyl; alkoxycarbonyl, such as t-butyloxycarbonyl (Boc) and carbobenzyloxy (Cbz); and α-aminoacyl residues, which may themselves be similarly N-protected. Other intended groups may be found in Volume 3 of The Peptides, E. Gross and J. Meinhofer, editors, Academic Press, 1981.

"Pharmaceutically-acceptable amide" refers to the pharmaceutically-acceptable, nontoxic amides of the compounds of the present invention which include amides formed with suitable organic acids or with amino acids, including short peptides consisting of from 1-to-6 amino acids joined by amide linkages which may be branched or linear, wherein the amino acids are selected independently from naturally-occurring amino acids, such as for example, glycine, alanine, leucine, valine, phenylalanine, proline, methionine, tryptophan, asparagine, aspartic acid, glutamic acid, glutamine, serine, threonine, lysine, arginine, tyrosine, histidine, ornithine, and the like.

"Pharmaceutically-acceptable ester" refers to the pharmaceutically-acceptable, nontoxic esters of the compounds of the present invention which include C_1-C_6-alkyl esters, wherein C_1-C_6-alkyl is as defined above, and C_5-C_7-cycloalkyl esters, wherein C_5-C_7-cycloalkyl refers to cyclic saturated hydrocarbon radicals, such as cyclopentyl, cyclohexyl, and the like. Also included are C_6-C_{12}-aryl-C_1-C_6-alkyl esters, wherein C_6-C_{12}-aryl-C_1-C_6-alkyl

are as defined above. Representative examples include benzyl, phenethyl, and the like.

"Pharmaceutically-acceptable salts" refers to the pharmaceutically-acceptable, nontoxic, inorganic or organic acid addition salts of the compounds of the present invention, as described in greater detail below.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compounds of Formula (I), as for example, by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, American Chemical Society (**1975**). Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of Bioreversible Carriers in Drug Design: Theory and Application, edited by E.B. Roche, Pergamon Press (**1987**).

The term "prodrug ester group" refers to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art.

The term "protecting group" is well known in the art and refers to sustituents on functional groups of compounds undergoing chemical transformation which prevent undesired reactions and degradations during a synthesis; see, for example, T.H. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, (**1981**).

"Substituted C_1-C_6-alkyl" refers to a C_1-C_6-alkyl group, as defined above, substituted with one substituent selected from C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-thioalkoxy, carboxy, carbo-C_1-C_4-alkoxy, nitro, halo-C_1-C_4-alkyl, hydroxy, amino, and C_1-C_4-alkylamino.

"Substituted C_6-C_{12}-aryl" refers to a substituted C_6-C_{12}-aryl group, as defined above, substituted with one, two, or three substituents independently selected from C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-thioalkoxy, carboxy, carbo-C_1-C_4-alkoxy, nitro, halo-C_1-C_4-alkyl, hydroxy, amino, and C_1-C_4-alkylamino.

"Substituted C_6-C_{12}-aryl-C_1-C_4-alkyl" refers to a C_6-C_{12}-aryl group, as defined above, appended to a C_1-C_4-alkyl radical, as defined above.

"Substituted C_6-C_{12}-aryloxy" refers to a substituted C_6-C_{12}-aryl group, as defined above, attached to a linking oxygen atom.

By a "therapeutically-effective amount" of the compound of the invention is meant a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention is to be decided by the attending physician within the scope of

sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts and well within the capabilities of attending physicians.

"Thioalkoxy", as used herein, refers to $R^{19}S$-, wherein R^{19} is either a C_1-C_4-alkyl group or a C_1-C_6-alkyl group, as specified.

The following abbreviations are used herein: BOC or Boc for t-butyloxycarbonyl, Boc_2O for di-t-butyloxydicarbonyl carbonate, Bz for benzyl, Cbz for benzyloxycarbonyl, $CDCl_3$ for deuterochloroform, CH_3CN for acetonitrile, CH_3I for methyl iodide, D_2O for deuterium oxide, DCC for dicyclohexylcarbodiimide, DIBAL for diisobutylaluminum hydride, DIEA for diisopropylethylamine, DMAP for dimethylaminopyridine, DMF for N,N-dimethylformamide, DMSO for dimethylsulfoxide, DMSO-d_6 for deuterodimethylsulfoxide, EDCI for 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride, EtOH for ethanol, Et_2O for diethyl ether, H_2O for water, HOAc for acetic acid, IBCF for isobutyl chloroformate, K_2CO_3 for potassium carbonate, KOH for potassium hydroxide, LAH for lithium aluminum hydride, Ms for methanesulfonyl, MsCl for methanesulfonyl chloride, $NaHCO_3$ for sodium hydrogen carbonate or sodium bicarbonate, NaOH for sodium hydroxide, NH_3 for ammonia, N_2H_4 for hydrazine, NH_4OH for ammonium hydroxide, NH_4OAc for ammonium acetate, NMM for N-methylmorpholine, PAW for pyridine/acetic acid/water (20:6:11), p-TsOH for p-toluene sulfonic acid, rt for room temperature, TBAF for tetrabutylammonium fluoride, TBDMS-Cl for t-butyldimethylsilyl chloride, TEA for triethylamine, TFA for trifluoroacetate, THF for tetrahydrofuran, TMSi for trimethylsilyl, and ϕCH_3 for toluene.

Amino acids are herein designated as the natural L-isomer or as the D-isomer in accordance with convention, or chiral compounds, including amino acids, are assigned the R, S, or (R,S) configuration at the chiral center. Preferred compounds of the present invention are those which have the S configuration at the alpha-carbon atom, *i.e.,* the carbon atom in the formula (I) designated by an *. The terms "R" and "S" configuration used herein are as defined by IUPAC (IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, *Pure Appl. Chem.*, **1976**, 45: 13-30.)

The compounds of the present invention can be used in the form of pharmaceutically-acceptable salts derived from inorganic or organic acids. These salts include, but are not limited to, the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, flavianate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

Appropriate cationic salts are also readily prepared by conventional procedures such as treating an acid of formula (I) with an appropriate amount of base, such as an alkali or alkaline earth metal hydroxide, e.g., sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, cyclohexylamine, dicyclohexylamine, triethylamine, piperidine, pyrrolidine, benzylamine, and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dialkyl sulfates; long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

The salts of the present invention can be synthesized from the compounds of formula I which contain a basic or acidic moiety by conventional methods, such as by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

When a compound of formula (I) is used in a human subject, the total daily dose administered in single or divided doses may be in amounts, for example, from about 0.01 to about 50 mg/kg body weight, or more usually, from about 0.2 to about 30 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administering to a patient in need of such treatment from about 20 mg to about 2000 mg of the compound(s) of this invention per day in multiple doses or in a single dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the particular treatment and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender and diet of the patient, the time of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically-acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Liquid dosage forms for oral administration may include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants, such as wetting agents; emulsifying and suspending agents; and sweetening, flavoring and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butandiol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The injectable formulation may be sterilized, as for example by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which may be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of a drug from subcutaneous or intramuscular injection. The most common way to accomplish this is to inject a suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug becomes dependent on the rate of dissolution of the drug which is, in turn,

dependent on the physical state of the drug, for example, the crystal size and the crystalline form. Another approach to delaying absorption of a drug is to administer the drug as a solution or suspension in oil. Injectable depot forms may also be made by forming microcapsule matrices of drugs and biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer and the composition of the polymer, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly-orthoesters and polyanhydrides. The depot injectables may also be made by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Suppositories for rectal administration of the drug may be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills may additionally be prepared with enteric coatings.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically-acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulations, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The present agents may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic physiologically acceptable and metabolizable lipid capable of forming liposomes may be used. The present compositions in liposome form may contain, in addition to the compounds of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Vol. XIV, Academic Press, New York, N. Y. **1976**, pp. 33 *et seq.*

The compounds of this invention may be administered alone or in combination or in concurrent therapy with other agents.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

Synthesis of the Compounds of the Invention

In general compounds of the current invention may be prepared in the following ways: starting with a D, L, or D,L β-hydroxy-α-aminoacid **1** (the R enantiomer at the α carbon center is shown for illustration) N-protected with a protecting group (P) of which Boc, Cbz, Fmoc, etc. are preferred, an ester **2**, where R = methyl (Scheme 1), can be prepared via diazomethane reaction. Alternatively compound **2** may be prepared by reacting the unprotected form of **1** with an appropriate alcohol ROH (e.g., MeOH under acidic conditions). The resulting amino acid ester hydrochloride is N-protected under standard conditions to provide **2** directly. Compound **2** is reacted under mild acid conditions (e.g., with p-TsOH) with an appropriate aldehyde, ketone, or acetal/ketal equivalent thereof ($(R^{13}(CO)R^{14}$) e.g., dimethoxypropane, benzaldehyde, cyclohexanone, etc.) to provide ester **3**. Ester **3** is converted to the aldehyde **4** either by direct reduction with DIBAL or via the fully reduced alcohol form (e.g., further reaction with DIBAL, LAH, etc.) followed by oxidation (Swern conditions, pyridine sulfur trioxide complex, etc.). The aldehyde **4** can serve as a precursor to the secondary alcohol **5** via reaction with an appropriate nucleophile (e.g., alkylmagnesium halides, alkenylmagnesium halides, alkynyllithium reagents, alkyllithium reagents, etc.). The alcohol **5** may be oxidized to the ketone **6** (e.g., Swern oxidation, pyridine sulfur trioxide complex, pyridinium chlorochromate, etc.). Either the aldehyde **4** or the ketone **6** can then be converted to enoate **7** via the appropriate Wittig, Horner Emmons reagent or their synthetic equivalents (e.g., alkyl (triphenylphosphoranylidene)acetate, etc.). For simplicity the trans-form of the C=C double bond is shown in this and the following schemes but it is obvious to one versed in the art that the cis form is available from alternative Horner Emmons type reagents / reactions. In the case where **7** arises from compound **4**, R^8 = H. The enoate **7** can be reduced to the allylic alcohol **8** or to the intermediate reduction product aldehyde **9**. Aldehyde **9** can also be obtained more directly via the oxidation of alcohol **8** under a number of conditions (vide supra). The aldehyde **9** can be converted to the alcohol **10** via reaction with organometallic nucleophiles (e.g., methylmagnesium bromide,

etc.). An alternative procedure to provide **10** wherein R^{10} is methyl is reaction of the aldehyde derived from ester **7** with a nucleophilic reagent (e.g., methyllithium, etc.). Compound **10** is equivalent to the alcohol **8** when R^{10} is hydrogen. The alcohol **10** is reacted with MsCl under basic conditions (TEA, etc.) to provide the mesylate **11**. The mesylate **11** is reacted with sodium azide to provide the azide **12a** or with phthalimide anion to provide the phthalimide **12b**. Azide **12a** can be reduced under a number of conditions (e.g., sodium borohydride, palladium catalyzed hydrogenation, triphenylphosphine followed by acid hydrolysis, etc.) to provide the amine **13**. Alternatively the phthalimide **12b** is reacted with N_2H_4 to provide the amine **13**. The amine **13** is guanylated with a variety of guanylation reagents (e.g., S-methyl N-nitrothiopseudothiourea, etc.) to provide the desired compound **14**. Alternatively the amine nitrogen can be protected with the N-protecting group (P') to provide the intermediate **15**.

Compound **15** is reacted with acid under hydrolytic conditions to remove the aldehydic/ketonic group ($R^{13}(CO)R^{15}$) (Scheme 1, continued) and provide the compound **16**. In some cases the N-protecting group (P) is labile and a second step of N-protection with (P) is required to provide **16**. The alcohol **16** can be oxidized to the compound **17**. When R^6 is hydrogen an oxidant is Jones reagent (Spaltenstein et al.*J. Org. Chem.*, 1987, *52*: 3759-66), and the resulting product **17** is a carboxylic acid (R^6 = OH, or ester equivalent: after esterification R^6 = alkoxy, etc.). The protecting group (P') of compound **17** is removed in a standard fashion to provide compound **18**. The amine **18** can be guanylated using various guanylation reagents to the provide the compound **19**. The protecting group (P) of compound **19** is removed to provide the desired compound **20**. In addition, compounds of the type **14** can be reacted under acidic hydrolytic conditions when (P) is an acid labile N-protecting group to provide the desired aminoalcohol **21**.

An alternative sequence which also provides the desired guanidino compounds is illustrated in Scheme 2. Compounds such as **13** can be reacted with cyanogen bromide under mild basic conditions (TEA, etc.) to provide the cyanamide **22**. An alternative sequence is the formation of the parent urea via reaction of **13** with trimethylsilylisocyanate or its equivalents (e.g., trichloroacetylisocyanate followed by basic removal of the trichloroacetyl group, etc.) and dehydration (e.g., tosylchloride in pyridine, etc.) of the parent urea to the cyanamide **22**. The cyanamide **22** is reacted with nucleophiles such as H_2NR^5 to provide the guanidino compound **23**. This sequence is particularly useful in the cases where (H_2NR^5 is N_2H_4, substituted N_2H_4, hydroxylamine, alkoxyamine, etc.). Likewise compound **23** can be transformed to compound **24**. In a manner similar to the transformation of **13** to compound **22**, compounds

such as **18** can be reacted with cyanogen bromide (alternatively via the sequence involving the intermediate urea form) to produce the cyanamide **25**. Compound **25** is converted to the guanidino compound **26** which in turn can be deprotected (loss of (P)) to produce the guanidino compound **27**.

Another approach to guanidino compounds is represented in Scheme 3. Compound **13** is reacted with diarylcyanocarbonimidate to provide compound **28** where in the ϕ symbol represents the aryl group. Compound **28** can be reacted with a nucleophile Y' to provide compound **29** where in R^5 may represent cyano or hydrogen. Likewise compound **18** can be reacted with diarylcyanocarbonimidate to yield **30**, and compound **30** can be reacted with the nucleophile Y' to produce compound **31**.

The approach outlined in Scheme 4 begins with readily available α-amino acids of either D,L, D or L configuration. The α-amino acids **32** are converted through a number of methods to the corresponding α-amino acid aldehyde **33**. For example, the dimethylpyrazolide of **32** is prepared and then reduced with LAH to provide **33**, or the ester of **32** can be reduced to the aldehyde directly via DIBAL reduction or the ester can be reduced fully to the alcohol state and the alcohol oxidized to the aldehyde **33**. The aldehyde **33** is reacted with alkenyl lithium reagents to provide the allylic alcohol **34**. Alternatively an alkynylorganometallic reagent may be added and this intermediate reduced to the corresponding allylic alcohol **34**. The alcohol is protected with an O-protecting group (e.g., Cbz, trialkylsilylgroups, etc.) to provide compound **35**. Compound **35** is oxidatively degraded to compound **36** via the action of ozone or as an alternative via the action of osmium tetroxide and sodium periodate. The compound **36** is condensed with a Wittig reagent (or Horner-Emmons reagent or their equivalents) to provide the enoate **37**. A preferred reagent when R^8 is hydrogen is an alkyl (triphenylphosphoranylidene)acetate or an alkyl (triphenylphosphoranylidene)-propionate. The enoate **37** is reduced via the action of DIBAL (or other reductants) to the allylic alcohol **38**. The allylic alcohol **38** is oxygen protected with a different protecting group (P") (eg.t-butyldimethylsilyl, t-butyldiphenylsilyl, trimethylacetyl, etc.) to provide compound **39**. The first O-protecting group (P') is selectively removed to provide compound **40**. Compound **40** is reacted under basic conditions with trichloroacetonitrile to provide an intermediate imidate which upon heating in xylene results in the formation of compound **41**. The amide **41** is converted to the guanidine **42** via a sequence of N-deprotection (removal of (P)) and guanylation. Alternatively the trichloroacetamide can be replaced with alternate N-protecting groups prior to or subsequent to the guanylation step to provide compound **42**. Finally compound **42** is fully deprotected via removal of both (P) and (P") to provide compound **43**.

Compound **41** may also be oxidized to α-aminoacid **44**. First the O-protecting group (P") is removed and the resulting alcohol treated with Jones reagent (or similar oxidant) to provide **44**. Compound **44** may then be transformed to the guanidine **45** in a similar fashion to the transformation of **41** to **42**. The guanidine **45** can be converted to the the α-aminoacid **46** via base treatment to remove the trichloroacetamide group.

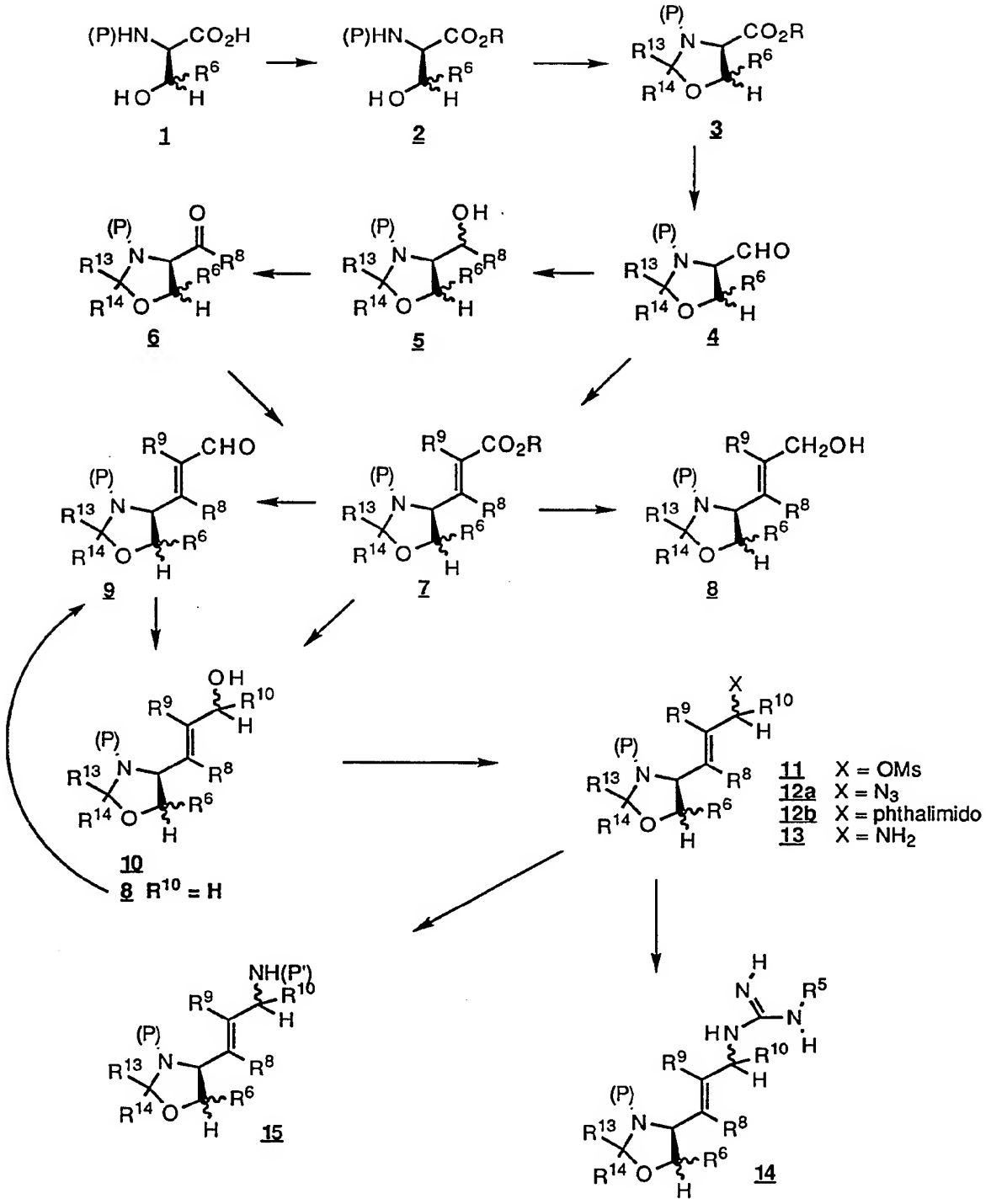
Scheme 5 illustrates the general synthetic paths that may be used to achieve guanylation of compounds; some of these methods have been illustrated in the previous schemes. An amine of general formula **47** (examples from previous schemes include, but are not limited to, compounds **13, 18** and the N-deprotected forms of compounds **41** and **44**) is reacted directly with S-methyl alkylthiopseudouronium salts, N-substituted aminoiminomethanesulfonic acids or the like (for example S-methyl N-methylthiopseudothiourea, S-methyl N-nitrothiopseudothiourea, N-ethyl aminoiminomethanesulfonic acid, etc.) to provide the product **48** directly. In specific cases where R^3 is equivalent to a carboxylic acid and NR^1R^2 is equivalent to a simple unprotected amine form, then prior complexation of compound **47** with a cupric salt can be accomplished. The cupric salt complex can then be reacted with the guanylating agent and subsequently the copper removed via the action of hydrogen sulfide (or its synthetic equivalents) to provide compound **48**. Guanylating reagents such as thiopseudouronium salts, aminoiminosulfonic acids, etc. can generally be prepared from literature sources via the intermediating corresponding urea or thiourea. Compound **47** can also be reacted with isocyanates or isothiocyanates to provide the compound **49**. An alternative approach to compound **49** is to first react the amine **47** with phosgene, thiophosgene, or their synthetic equivalents followed by reaction with the amine H_2NR^5 providing compound **49** in two sequential steps. In either of these cases, the parent urea or thiourea produced may be alkylated to provide an intermediate isourea or isothiourea form, which when reacted with the nucleophile NH_2R^5, provides the compound **48**. In this alkylative sequence to produce the desired **48**, a thiourea form is preferred owing to the ease of alkylation. In some cases, for compound **49**, R^5 may represent a protecting groups (e.g., Cbz, benzoyl, etc.) which can be removed subsequent to the reaction with NH_2R^5 to provide the product **48**.

Compound **47** is reacted with cyanogen bromide to provide the cyanamide **50**. Cyanamide **50** can also be produced via dehydration of the urea form of **49** in the particular case when R^5 is hydrogen. The cyanamide **50** is reacted with the nucleophile H_2NR^5 to provide the desired **48**.

Another specific synthetic transformation outlined in Scheme 6 is the conversion of nitroguanidino compounds to their corresponding aminoguanidino and guanidino derivatives. For example compounds containing the substructure nitroguanidine represented by **51** are reduced in the presence of zinc and acetic acid to provide the aminoguanidine compounds represented by substructure **52**. Full reduction of the nitroguanidine **51** provides the guanidine compound represented by substructure **53**.

Compounds of the aminoalcohol type represented by **21**, **24**, and **43** may be reacted with various N-protecting groups (P) to provide additional compounds envisioned by the invention. It is also envisioned that aminoalcohols and their N-protected amino alcohol analogs represented for instance by structures **21**, **24**, and **43**, may also be converted to their cyclic acetal forms via the action of an appropriate acetal, ketal, or their synthetic equivalents under acidic conditions to provide compounds of the invention. In these cases coupling to provide polypeptide structures which contain the above substructures are specifically envisioned. Compounds containing the α–aminoacid substructure for instance **17**, **19**, **20**, **26**, **27**, **31**, and **45** can also be employed in polypeptide formation in a standard manner and the resulting products are additionally envisioned within the scope of this invention.

Scheme 1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HO R6 H
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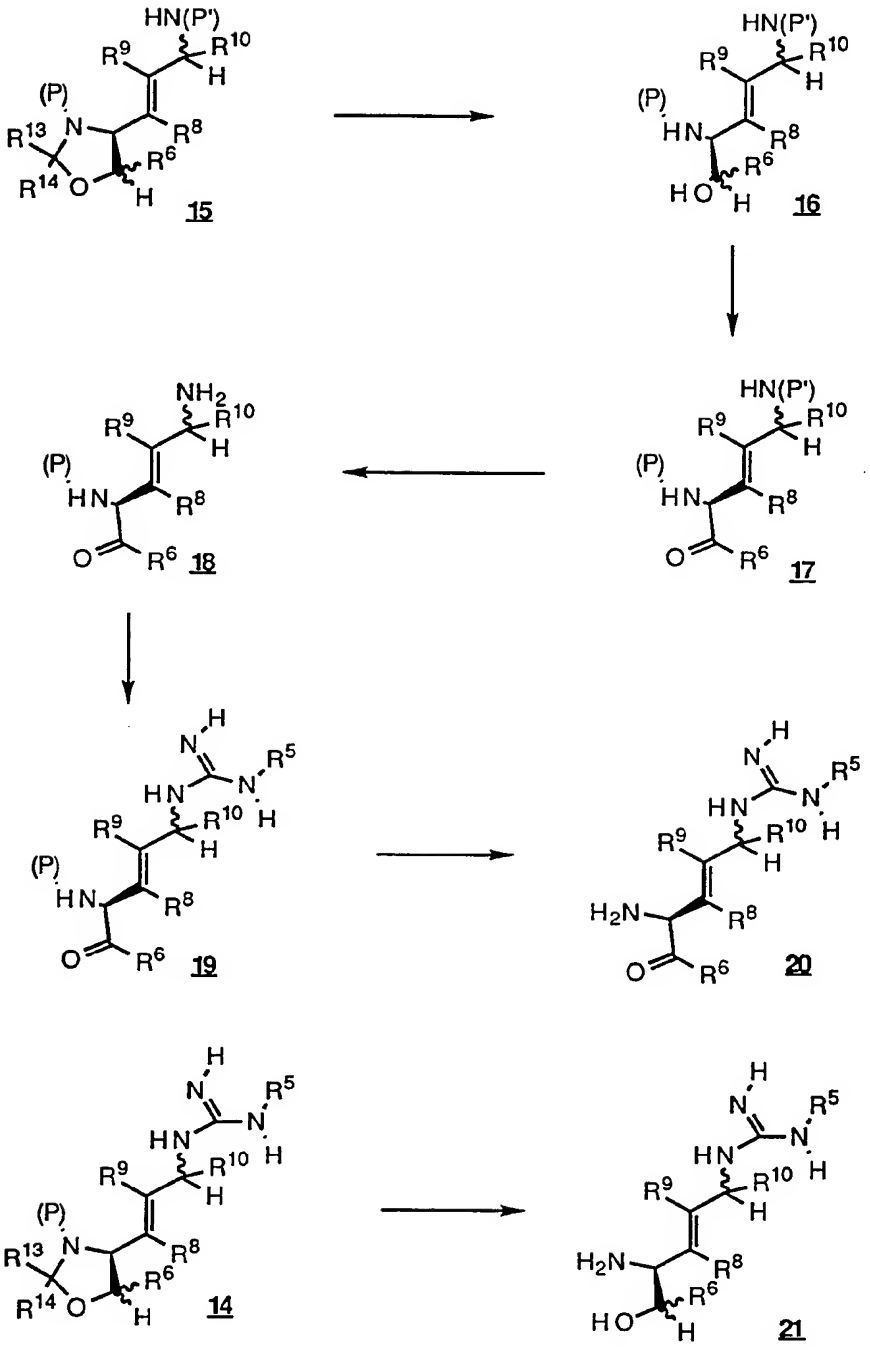
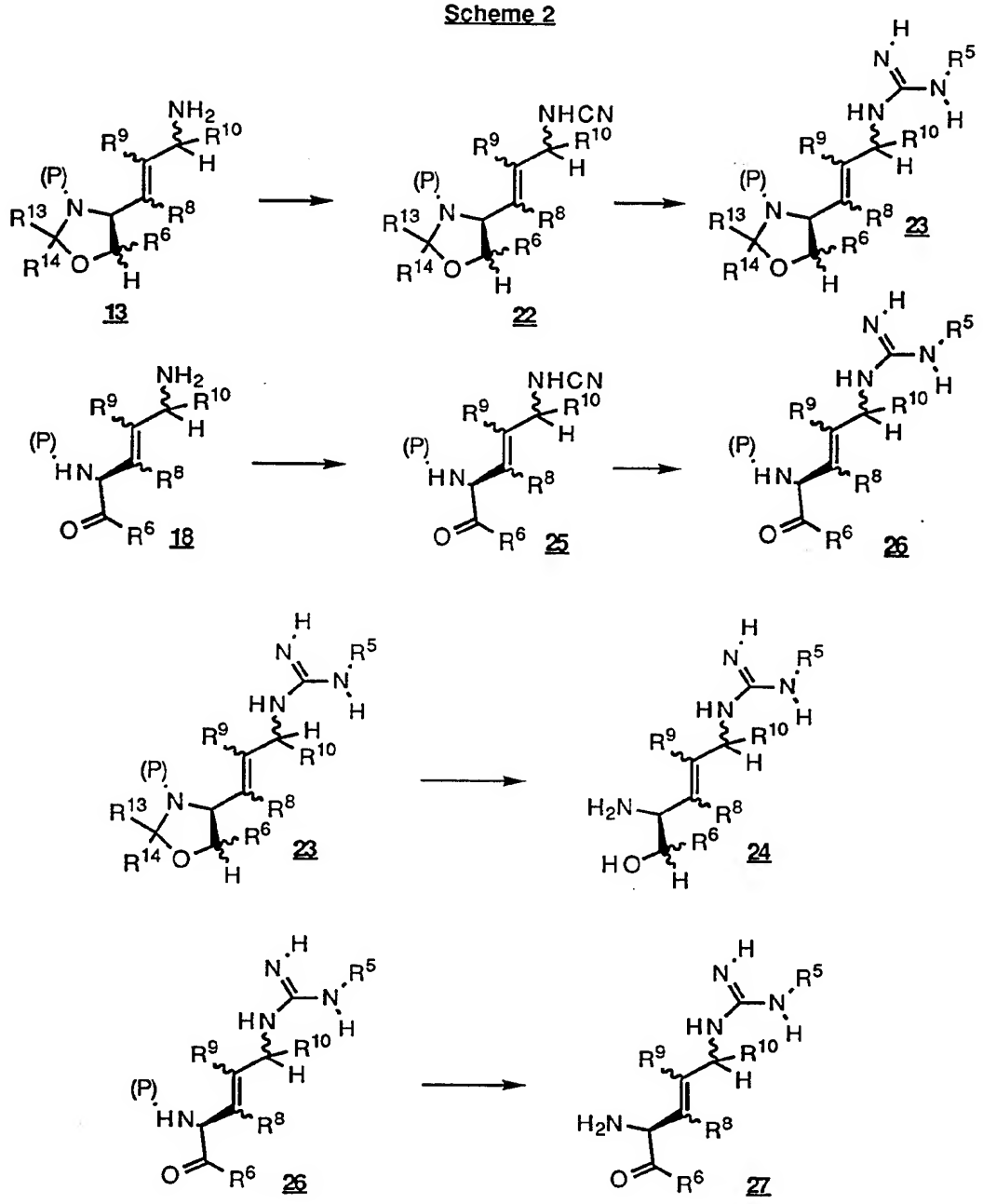
(P)HN CO2R
HO R6 H
2
(P) N CO2R
R13 R14 O R6 H
3
(P) N CHO
R13 R14 O R6 H
4
(P) N OH R6R8
R13 R14 O H
5
(P) N O R6R8
R13 R14 O H
6
R9 CO2R
(P) N R8
R13 R14 O R6 H
7
R9 CHO
(P) N R8
R13 R14 O R6 H
9
R9 CH2OH
(P) N R8
R13 R14 O R6 H
8
OH R10
R9 H
(P) N R8
R13 R14 O R6 H
10
8 R10 = H
X R10
R9 H
(P) N R8
R13 R14 O R6 H
11 X = OMs
12a X = N3
12b X = phthalimido
13 X = NH2
NH(P') R10
R9 H
(P) N R8
R13 R14 O R6 H
15
H N R5
HN N H
R9 R10 H
(P) N R8
R13 R14 O R6 H
14

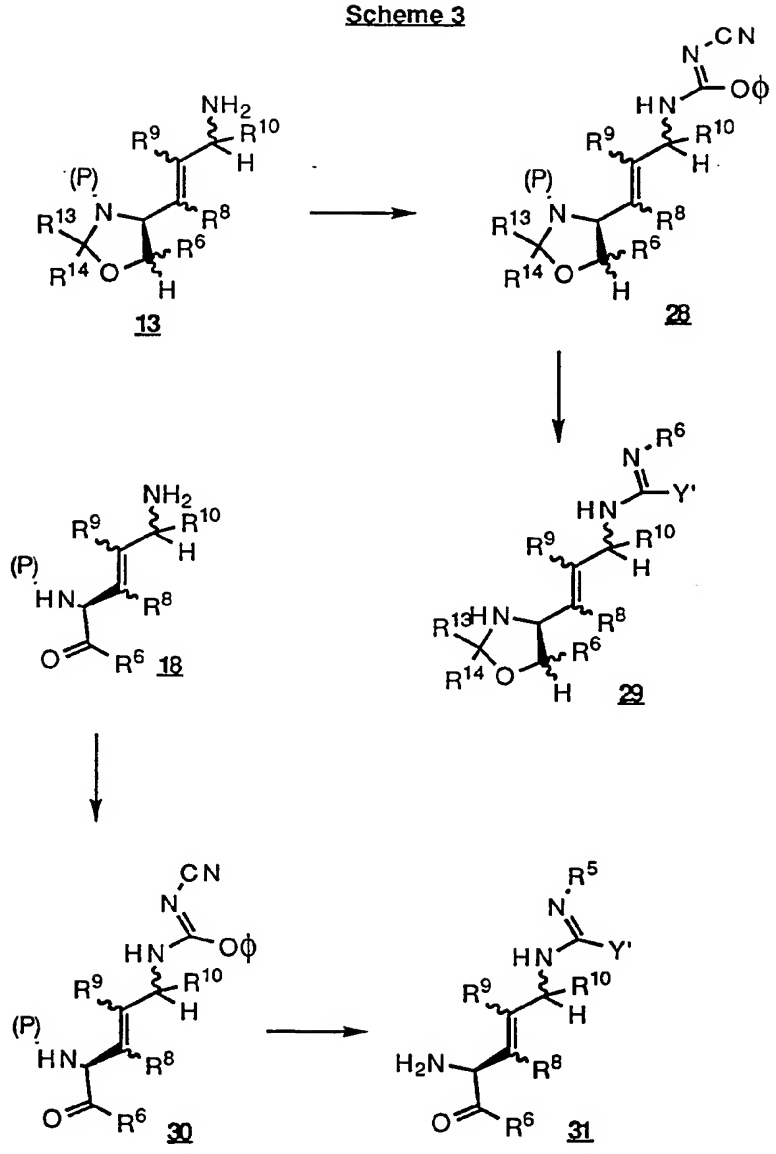
Scheme 1 (con't)



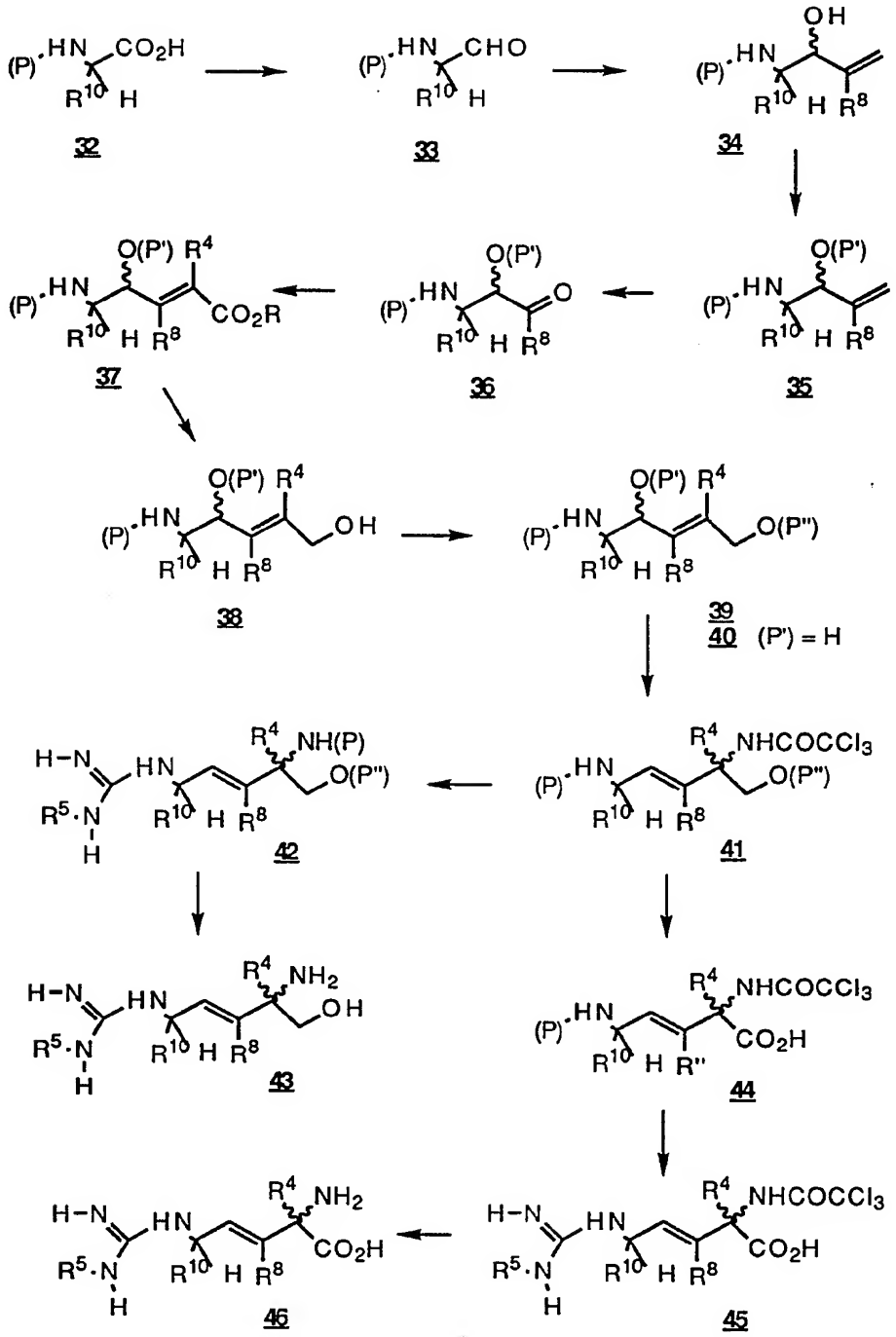
Scheme 2



Scheme 3



Scheme 4


(P)·HN CO2H
R10 H
32
(P)·HN CHO
R10 H
33
OH
(P)·HN
R10 H R8
34
O(P')
(P)·HN
R10 H R8
35
O(P')
(P)·HN
R10 H R8
O
36
O(P') R4
(P)·HN
R10 H R8
CO2R
37
O(P') R4
(P)·HN
R10 H R8
OH
38
O(P') R4
(P)·HN
R10 H R8
O(P")
39
40 (P') = H
R4 NHCOCCl3
(P)·HN
R10 H R8
O(P")
41
R4 NHCOCCl3
(P)·HN
R10 H R"
CO2H
44
R4 NHCOCCl3
H-N
HN
R5·N
H
R10 H R8
CO2H
45
R4 NH(P)
H-N
HN
R5·N
H
R10 H R8
O(P")
42
R4 NH2
H-N
HN
R5·N
H
R10 H R8
OH
43
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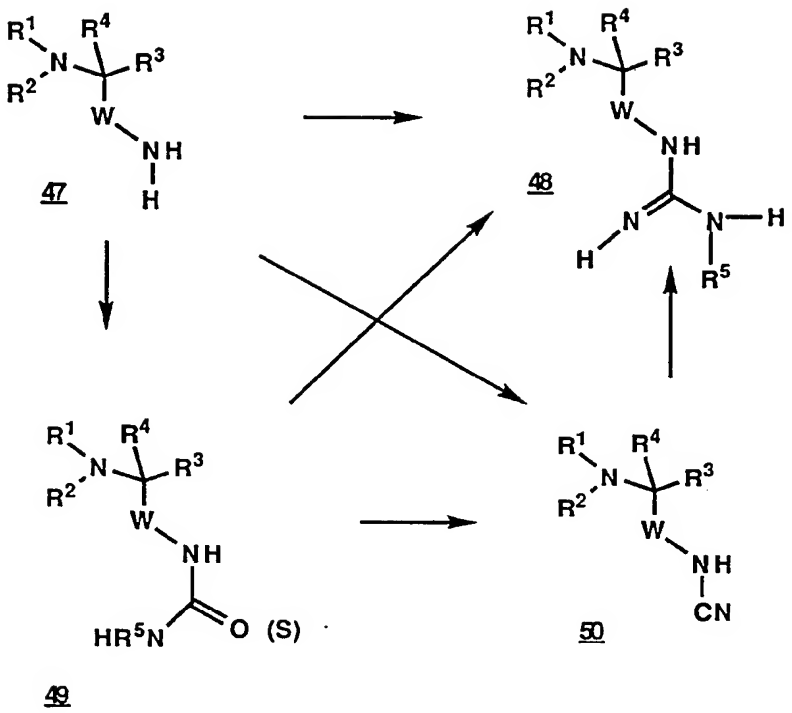
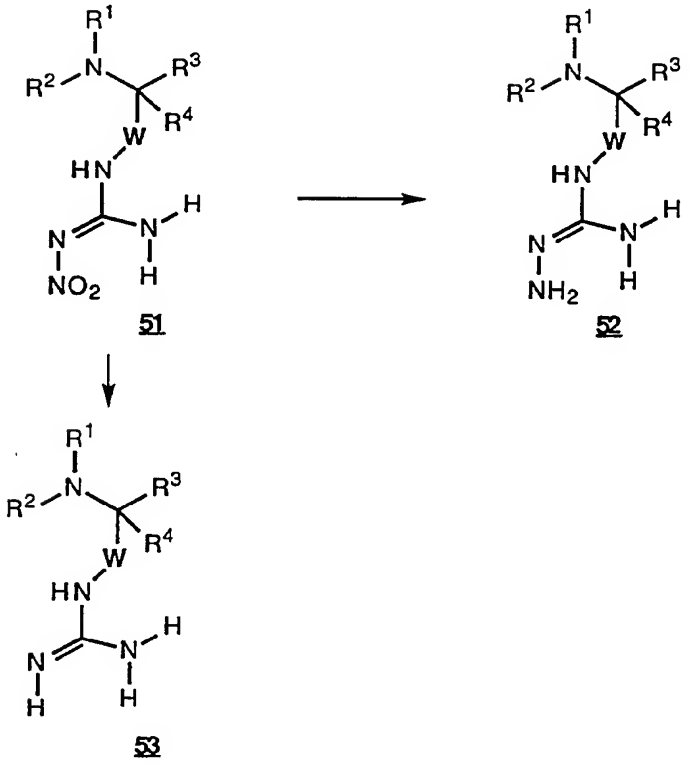
H-N
HN
R5·N
H
R10 H R8
CO2H
46

Scheme 5



Scheme 6



General Experimental Procedures for Bioassays

It is known that NO synthase utilizes L-arginine to produce NO and the by-product citrulline. By measuring the conversion of [^{3}H]-L-arginine to [^{3}H]-L-citrulline, the enzyme activity can be monitored. In the presence of [^{3}H]-L-arginine, an inhibitor would lower the conversion rate, and a substrate would compete with L-arginine and likewise lower the conversion rate. Compounds which reduce citrulline production in this assay are therefore modulators of NO synthase activity.

[^{3}H]-Arginine to [^{3}H]-Citrulline Conversion

The conversion of L-arginine to L-citrulline was assayed as reported previously (Bredt and Snyder, *Proc. Nat'l Acad Sci USA*, 1989, *87*: 682-5), with minor modifications. Briefly, samples of partially-purified NO synthase, 50-100 µg or 20 µL (alternatively cytosolic preparations from RAW 264.7 cells, a murine monocyte-macrophage cell line, induced for 16 hours with 10 µg/mL medium of Lipopolysaccharide (LPS), or partially-purified (phosphocellulose column) type Ia isozyme from rat brain cerebellum, or partially-purified isozyme III from bovine aortic endothelial cells (BAE cells)) were incubated for 20 minutes (3 minutes in the cases of purified enzyme preparations) at 25°C in the presence of 10 mM L-[2,3-^{3}H]arginine (55 C_i/mmol) (containing 34 nM (0.2 µC_i)), 1 mM NADPH, 100 nM calmodulin, 2 mM $CaCl_2$, and 3 µM tetrahydrobiopterin (BH_4) in a final volume of 100 µL. The reaction was stopped by adding 1 mL of stop buffer (2 mM EGTA, 2 mM EDTA, 20 mM Hepes, pH 5.5). The total volume was then applied to a 1 mL Dowex AG 50WX-8 column (Na^+ form, Bio-Rad) that had been pre-equilibrated with the stop buffer. L-[2,3-^{3}H]Citrulline was eluted (2x) with 0.5 mL of stop buffer and radioactivity was determined by liquid scintillation counting. The L-[2,3-^{3}H]arginine (Dupont, NEN) was purified prior to use on Dowex AG-1-X8 ($CH_3CO_2^-$ form, Bio-Rad), eluted with distilled water, acidified, concentrated on a Speed-Vac (Savant) and stored at -20°C. Table I, below, presents data on the percent inhibition of [^{3}H]-L-citrulline formation by the compounds of the invention. Table II presents data showing the potencies of the compounds.

Table I

Percent Inhibition of [^{3}H]-Citrulline Formation at 100μM

Example No.	Rat Brain Cytosol	RAW Cell Cytosol	BAE Preparation
1	6	0	nd
2	80	14	nd
3	35	68	nd
4	30	50	22
6	0**	46*	0**
7	nd	17	nd
8	23	13	nd
9	51	47	nd
10	74	43	40
11	20	41	nd
12	70	8	5
14	0	0	nd
15	90	66	50
17	18	6	nd
18	17	9	nd
19	77	27	0
20	27	45	nd
21	86	94	50
22	70	97	50
24	35	20	nd
25	80	20	14
27	86	97	46
30	13	25	nd
31	92	55	nd
33	88	74	nd
35	nd	50	nd
37	nd	61	nd
38	88	69	nd
39	11	0	nd
40	nd	3	nd
42	22	nd	nd
43	29	0	nd
44	21	25	nd

* tested at 10 μM

** tested at 30 μM

Table II

Inhibition of [^{3}H]-Citrulline Formation IC_{50} (μM)

Example No.	Rat Brain Cytosol	RAW Cell Cytosol	BAE Preparation
1	>100	>100	>100
2	40	>100	80
3	>100	40	>100
4	>100	100	>100
6	>30	22	>30
7	nd	>100	nd
8	>100	>100	nd
9	80	100	nd
10	30	>100	>100
11	>100	>100	nd
12	30	>100	>100
14	>100	>100	>100
15	10	40	100
17	>100	>100	nd
18	>100	>100	nd
19	35	>100	>100
20	>100	100	nd
21	20	30	100
22	40	<100	100
24	>100	>100	nd
25	40	>100	>100
27	20	20	>100
30	>100	>100	nd
31	3	75	72
33	10	35	55
35	50	100	>100
37	5	60	80
38	9	45	>100
39	>100	>100	nd
40	40	>100	nd
42	>100	nd	nd
43	>100	>100	nd
44	>100	>100	nd

cGMP Assay - (Rat Fetal Lung Fibroblast (RFL-6) cells as detectors of EDRF/NO)

The method of Ishii *et al.*, (*American Journal of Physiology*, **1991**, 261(2 Pt 2), H598-603) was followed to detect and quantify EDRF. This bioassay technique for EDRF and NO is sensitive, simple, and quite useful for the evaluation of compounds that regulate EDRF release from various endothelial cells, tissues, and NOS enzymes. Cyclic GMP responses of RFL-6 rat fetal lung fibroblast cells were utilized to estimate the activity of nitric oxide synthase (NOS) and EDRF. The conditioned medium from bovine aortic endothelial (BAE) cells cultured in tissue culture plates (alternatively cytosolic preparations from a murine macrophase cell line--RAW cells--induced for 16 hours with 10 µg/mL medium of LPS, or partially purified (phosphocellulose column) type I isozyme from rat brain cerebellum, or partially purified isozyme III from BAE cells) was quickly transferred to RFL-6 incubations in order to determine NO. In the case of enzyme preparations RFL cells are incubated directly with the preparation. In the presence of superoxide dismutase, RFL-6 cells cultured in 6-well tissue culture plates exhibited very high sensitivities to both NO and EDRF: e.g., they responded to NO at a concentration as low as 2 nM and the basal release of EDRF from 1-2 x 10^6 BAE cells.

RFL-6 Cell Culture Method

Rat fetal lung fibroblast cells (RFL-6, Stanford University, CA) were grown in 6-, 12-, 24- or 48-well tissue culture plates containing F-12 Ham's nutrient mixture supplemented with 15% uninactivated fetal bovine serum. Bovine aortic endothelial (BAE) cells (NIGMS, Human Genetic Mutant Cell Repository, Camden, NJ) were cultured in the 6-well plates containing Eagle's Minimum Essential Medium (MEM) supplemented with 20% fetal bovine serum and MEM nonessential amino acids (0.1 mM each). Both culture media contained 2 mM L-glutamate, 100 U/mL penicillin and 0.1 mg/mL streptomycin. Cells were maintained at 37°C under an atmosphere of 95% air: 5% CO_2.

Detection of EDRF/NO with RFL-6 Cells

BAE cells (RAW cells [induced with LPS], N1E-115 cells, rat brain homogenate passed through a phosphocellulose column, etc.) grown to confluence in 6-well plates were used as the source of EDRF/NO. After removing the culture medium, cells were washed twice with 2 mL of Lockes solution (without IBMX) and equilibrated for 20 minutes in 1 mL of Lockes buffer containing 20 U/mL of SOD in the presence or absence of 100 µM L-arginine, N^G-nitro-L-arginine (NNA), or the test compounds for 15 min before stimulation with 3 µM ADP for 3 minutes (no stimulation is necessary for homogenate

sources of enzyme or those cells induced with LPS, neurotensin is used to stimulate N1E-115 cells). Following exposure of BAE cells to ADP for 3 minutes, an aliquot of the conditioned medium was transferred to the RFL-6 incubations with a Pipetman® micropipette. Volumes of the conditioned medium transferred were 1000 µL, 400 µL, 200 µL and 100 µL when RFL-6 cells were incubated in the 6-, 12-, 24- and 48-well plates, respectively.

Before transferring the conditioned medium from BAE cells, RFL-6 cells cultured to confluence were washed twice with a Ca- and Mg-free PBS then equilibrated in Locke's buffer (with 0.3 mM IBMX, 20U/mL of SOD). The volume for preincubation was 500 µL - 1000 µL. After incubating RFL-6 cells with conditioned medium from BAE cells (or other EDRF/NO producing systems) for the indicated time periods (~ 3 minutes), the medium was removed and ice-cold 50 mM sodium acetate buffer (pH 4.0) was added to each well to stop the reaction followed by liquid nitrogen. Cyclic GMP levels in RFL-6 cells were determined by RIA (radioimmunoassay) or samples could be stored at -70°C until radioimmunoassay.

For assaying pure enzyme or homogenates containing active enzyme, the following alterations are made in the procedure: after preparation of the RFL cells by preincubation, a fresh Lockes buffer is added containing SOD and IBMX as before. In addition L-arginine (100 µM), NADPH (100 µM), BH_4 (3 µM), calmodulin (100 u/mL when necessary) and the test compound(s) are added followed by the enzyme homogenate to a final adjusted volume of 1-2 mL. Incubations proceed at 37°C for 3 minutes followed by the same termination steps as above. cGMP is again measured by RIA.

Since the cyclic GMP measured is an indirect measure of the amount of NO produced by NO synthase, compounds that reduce the amount of cyclic GMP are termed inhibitors of NO synthase and those that increase cyclic GMP in the absence of exogenous L-arginine are termed substrates or stimulators of NO synthase. Table III presents data illustrating that compounds of the invention are effective inhibitors of NO synthase activity, and not competitive substrates of the enzyme.

Table III

Inhibition of cGMP Formation in RFL Cells IC_{50} (µM)

Example No.	Rat Brain Cytosol	RAW Cell Cytosol	BAE Preparation
10	200	nd	nd
15	20	nd	nd
31	19	783	267

The following examples, which are provided for illustration and not limitation of the invention, will serve to further illustrate preparation of the novel compounds of the invention.

Example 1

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-nitroguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

Step 1a. N-[(1,1-Dimethylethoxy)carbonyl]-D-serine methyl ester

To a solution of D-Boc-serine (5.13 g, 25 mmol) in EtOH cooled to 0°C was added diazomethane (4-5 eq) in a solution of Et_2O. After the addition of the diazomethane, the reaction mixture was stirred for one hr and then quenched with glacial HOAc. The product was extracted with EtOAc. The combined organic extracts were washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography eluting with hexane/EtOAc (1:1) afforded the product (72%) as a yellow liquid: R_F 0.75 (EtOAc:hexane 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 2.48 (s, 1H), 3.82 (s, 3H), 3.90 (dd, J=4, 12 Hz, 1H), 3.95 (dd, J=4,12 Hz, 1H), 4.40 (m, 1H), 5.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2, 52.5, 55.6, 60.4, 63.1, 80.2, 155.7, 171.4; MS(DCI) *m/e* 220 $(m+H)^+$, 237 $(m+NH_4)^+$. Analysis calc'd for $C_9H_{17}NO_5 \cdot 0.5\ H_2O$: C 47.36; H 7.95; N 6.14. Found: C 47.20; H 7.58; N 6.12.

Step 1b. 3-(1,1-Dimethylethyl) 4-methyl-(R)-2,2-dimethyl-3,4-oxazolidinecarboxylate

To a solution of the methyl ester of Example 1a (1.05 g, 4.8 mmol) in benzene was added 2-methoxypropane (1.0 g, 2 eq) and p-TsOH (0.914 g, 0.1 eq), and the reaction mixture was heated to reflux for 48 hr. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with brine and H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography eluting with EtOAc and hexane afforded the product as a yellow liquid in 78% yield: R_F 0.5 (1:1 hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 1.55 (br s, 3H), 1.64 (s, 3H), 3.80 (s, 3H), 4.25 (m, 1H), 4.38 (dd, J=5, 9Hz, 1H), 4.50 (dd, J=6, 8.5 Hz, 1H); MS(DCI) *m/e* 260 $(m+H)^+$, 277 $(m+NH_4)^+$, 221 $(m-C_4H_9)$. Analysis calc'd for $C_{12}H_{21}NO_5 \cdot 0.75\ CH_2Cl_2$: C 46.56; H 6.90; N 4.22. Found: C 46.86; H 6.67; N 4.29.

Step 1c. 1,1-Dimethylethyl (R)-4-formyl-2, 2-dimethyl-3-oxazolidinecarboxylate

To a solution of the methyl ester of Example 1b (4.61 g, 17.8 mmol) in ϕCH_3 cooled to -78°C was added 1 M DIBAL (2.2 mL, 2.2 eq) over a 15-20 minute

period. The reaction was stirred for 3-4 hr at -78°C and then quenched with MeOH at -78°C. The reaction was extracted with EtOAc and the combined organic extracts were washed with NaOH, H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the product as a colorless oily solid (64%): R_F 0.45 (1:1 EtOAc:hexane); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.49 (s, 9H), 1.52 (s, 3H), 1.58 (s, 3H), 3.80 (m, 1H), 4.20 (m, 1H), 4.40 (m, 1H), 9.53 (br s, 1H); MS(DCI) *m/e* 230 $(m+H)^+$, 247 $(m+NH_4)^+$, 191 $(m-C_4H_9)$; $[\alpha]_D^{20}$ = -24.72° (c=1.0, EtOH).

Step 1d. 3-(1,1-Dimethylethyl)-(S)-4-(3-(ethoxypropen-2E-oyl))-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the aldehyde of Example 1c (9.27 g, 40.5 mmol) (which was freshly prepared) in THF at ambient temperature was added ethyl (triphenylphosphoranylidene)acetate (21.14 g, 1.5 eq). The reaction was stirred at ambient temperature for 4-6 hr and then concentrated *in vacuo*. Purification by flash chromatography eluting with hexane-EtOAc afforded the title compound as a colorless crystalline solid (83%): R_F 0.6 (1:1 EtOAc:hexane); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.29 (t, J=7 Hz, 3H), 1.42 (s, 9H), 1.51-1.63 (m, 6H), 3.82 (dd, J=3, 9.6 Hz, 1H), 4.10 (dd, J=7.5, 12.6 Hz, 1H), 4.20 (m, 2H), 4.40 (m, 0.5H), 4.60 (m, 0.5H), 5.83 (bt, J=15 Hz, 1H), 6.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.1, 122.3, 94.4, 80.2, 67.2, 60.4, 28.3, 27.2, 26.4, 24.6, 23.5, 14.2; MS(DCI) *m/e* 300 $(m+H)^+$, 317 $(m+NH_4)^+$, 261 $(m-C_4H_9)$, 200 (m+H-Boc). Analysis calc'd for $C_{15}H_{25}NO_5$ • 0.10 EtOAc • 0.20 H_2O: C 59.32; H 8.47; N 4.49. Found: C 59.27; H 8.52; N 4.73.

Step 1e. 3-(1,1-Dimethylethyl)-(S)-4-(3-hydroxypropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the ethyl ester from Example 1d (18.47 g, 61.8 mmol) in anhydrous ϕCH_3 cooled to -78°C was added DIBAL (309 mL, 5 eq) over a 30 minute period. The reaction was stirred at -78°C for 3 hr while following by tlc and then quenched at -78°C with MeOH. The product was extracted with EtOAc and the combined organic extracts washed with NaOH, H_2O, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography with hexane/EtOAc (1:1) afforded the product as a colorless oil (98%): R_F 0.30 (1:1 EtOAc:hexane); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 1.53 (s, 3H), 1.61 (s, 3H), 3.75 (dd, J=4.5, 9.0 Hz, 1H), 4.05 (dd, J=9.0, 16.0 Hz, 1H), 4.20 (d, J=5 Hz, 2H), 5.70 (m, 2H); MS(DCI) *m/e* 258 $(m+H)^+$, 275 $(m+NH_4)^+$, 219 $(m-C_4H_9)$; Analysis calc'd for $C_{13}H_{23}NO_4$ • 0.25 CH_2Cl_2: C 60.68; H 9.01; N 5.44. Found: C 60.31; H 8.64; N 5.19.

Step 1f. 3-(1,1-Dimethylethyl)-(S)-4-(3-mesyloxypropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the alcohol from Example 1e (3.08 g, 12.0 mmol) in CH_2Cl_2 at 0°C was added TEA (2.42 g, 2 eq) and MsCl (2.05 g, 1.5 eq). The reaction was stirred at 0°C for 30 minutes and then extracted with CH_2Cl_2. The combined organic extracts were washed with cold H_2O, cold 10% HCl, $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography eluting with hexane/EtOAc (1:1) afforded the title compound as a colorless liquid (84%): R_F 0.65 (1:1 EtOAc:hexane); ^1H NMR(300 MHz, $CDCl_3$) δ: 5.70 (m, 1H), 4.73 (bd, J=6.0 Hz, 2H), 4.18 (dd, J=7.5, 12 Hz, 1H), 3.75 (dd, J=3.5, 9 Hz, 1H), 3.10 (s, 2H), 1.60 (m, 3H), 1.57 (s, 3H), 1.52 (s, 3H), 1.48 (s, 9H); MS(DCI) *m/e* 336 $(m+H)^+$, 353 $(m+NH_4)^+$, 297 $(m - C_4H_9+NH_4)^+$; Analysis calc'd for $C_{14}H_{25}NO_6S$: C 50.13; H 7.51; N 4.18. Found: C 49.69; H 6.29; N 4.73.

Step 1g. 3-(1,1-Dimethylethyl)-(S)-4-(3-azidopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the mesylate from Example 1f (6.37 g, 19 mmol) at ambient temperature in MeOH/H_2O (10:1) was added sodium azide (1.48 g, 1.2 eq). The reaction was stirred for 2 hr and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography eluting with hexane/EtOAc (1:1) afforded the title product as a colorless oil (76%): R_F 0.65 (1:1 hexane:EtOAc); ^1H NMR(300 MHz, $CDCl_3$) δ: 5.75 (m, 2H), 4.4 (m, 1H), 4.08 (dd, J=6, 14 Hz, 1H), 3.80 (m, 3H), 1.60 (s, 3H), 1.55 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 124.8, 68.1, 58.4, 52.0, 28.4, 27.4, 26.6, 24.4, 24.7, 23.6, 23.5; MS(DCI) *m/e* 283 $(m+H^+)$, 300 $(m+NH_4^+)$, 244; Analysis calc'd for $C_{13}H_{22}N_4O_3 \cdot 0.15\ CH_2Cl_2$: C 53.53; H 7.62; N 18.99. Found: C 53.64; H 7.80; N 18.66.

Step 1h. 3-(1,1-Dimethylethyl)-(S)-4-(3-aminopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the azide from Example 1g (4.00 g, 14.2 mmol) in isopropanol at ambient temperature was added sodium borohydride (1.5 g, 3 eq). The reaction was heated at reflux for 24 hr, followed by tlc and extracted with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography eluting with EtOH/H_2O (2:1) containing 3% NH_4OH afforded the title compound as a colorless liquid (67%): R_F 0.30 (2:1 EtOH:H_2O containing 3% NH_3); ^1H NMR(300 MHz, $CDCl_3$) δ: 5.72 (m, 1H), 5.58 (dd, J=7.5, 15 Hz, 1H), 4.37 (bd, 2H), 4.05 (dd, J=5.0, 9.0 Hz, 1H), 3.73 (dd, J=1.8, 9 Hz, 1H), 3.32 (dd, J=1, 5.5 Hz, 2H),

1.58 (s, 3H), 1.56 (s, 3H), 1.45 (s, 9H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 128.2, 93.7, 79.4, 68.2, 58.7, 43.4, 28.4, 27.7, 26.5, 24.7, 23.6; MS(DCI) *m/e* 201 $(m-C_4H_9)^+$, 257 $(m+H)^+$; $[\alpha]_D^{20}$ = +49.29° (c=0.355, CH_2Cl_2); Analysis calc'd for $C_{13}H_{24}N_2O_3$: C 60.91; H 9.44; N 10.93. Found: C 57.23; H 9.43; N 10.31.

Step 1i. 3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-nitroguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the amine from Example 1h (0.040 g) in EtOH/H_2O (1:1) was added the N-nitro-S-methylpseudothiourea (0.017 g, 1 eq) and TEA (0.017 g, 1 eq). The reaction was stirred at ambient temperature for 48 hr and then concentrated *in vacuo*. Purification by flash chromatography eluting with EtOAc:CH_2Cl_2 (3:1) afforded the title compound as a white solid (90%): R_F 0.75 EtOAc:CH_2Cl_2 (3:1); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.42 (s, 9H), 1.45 (s, 3H), 1.53 (s, 3H), 3.69 (dd, J=1.2, 5.1 Hz, 1H), 3.83 (m, 2H), 4.02 (m, 1H), 4.31 (t, J=3Hz, 1H), 5.65 (m, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 23.5, 25.2, 26.95, 28.4, 43.1, 58.8, 67.9, 93.9, 127.9, 132.9, 152.3, 160.4; MS(DCI) *m/e* 344 $(m+H)^+$, 299, 244 $(m-Boc+H)^+$; MS(FAB) *m/e* 344 $(m+H^+)$; $[\alpha]_D^{20}$ = +42.71° (c=1.25, H_2O); Analysis calc'd for $C_{14}H_{25}N_5O_5$: C 48.97; H 7.34; N 20.40. Found: C 49.01; H 7.46; N 20.20.

Example 2

N^G-Nitroguanidinyl-4(S)-amino-pent-2,E-ene-5-ol

A solution of the product from Example 1i in 3N HCl in 66% HOAc was stirred at rt for 24 hr. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography over silica gel using CH_3CN/HOAc/H_2O (6/1/1) as the elutant. The yield was 62%: R_F 0.35 (CH_3CN/HOAc/H_2O; 6/1/1); $[\alpha]_D^{20}$ = +6.18° (c=0.10, MeOH); $[\alpha]_D^{20}$ = +23.62° (c=0.10, H_2O); ^1H NMR (300 MHz, D_2O) δ: 3.66 (dd, J=11.7, 6.3 Hz, 1H), 3.83 (dd, J=11.7, 3.6 Hz, 1H), 3.97 (m, 3H), 5.70 (dd, J=15.5, 7.5 Hz, 1H), 6.00 (dt, J=15.5, 4.5 Hz, 1H); ^{13}C NMR(75 MHz, D_2O) δ: 44.8, 56.9, 64.3, 126.7, 134.7, 161.8; MS(DCI) *m/e* 204 $(m+H)^+$; Analysis calc'd for $C_6H_{13}N_5O_3 \cdot 6\ HCl \cdot 0.80\ H_2O$: C 16.51; H 4.76; N 16.05. Found: C 16.58; H 4.64; N 15.91.

Example 3

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the amine from Example 1h (0.0817 g) in EtOH/H_2O (2:1) (10 mL) at ambient temperature was added S-methylpseudothiouronium sulfate (0.1182 g, 1.33 eq) and TEA (0.0646 g, 2 eq). The reaction was stirred at rt for 72 hr and then concentrated *in vacuo*. Purification of the residue by flash chromatography eluting with EtOAc:CH_2Cl_2 (3:1) afforded the product as a colorless oil (62%): R_F 0.50 (EtOH:H_2O, 2:1); ^1H NMR (300 MHz, CD_3OD) δ: 1.47 (s, 9H), 1.52 (s, 3H), 1.56 (s, 3H), 3.70 (dd, J=1.6, 7.8 Hz, 1H), 3.80 (d, J=3.4 Hz, 2H), 4.10 (dd, J=5.3, 11.0 Hz, 1H), 4.40 (m, 1H), 5.63 (m, 2H); MS(FAB/MAT90) *m/e* 299 ($m+H^+$); $[\alpha]_D^{20}$ = +19.42° (c=0.80, EtOH); Analysis calc'd for $C_{14}H_{26}N_4O_3$: C 49.68; N 8.46; N 13.63. Found: C 49.76; H 8.32; N 13.97.

Example 4

1-Guanidinyl-4(S)-amino-pent-2,E-ene-5-ol

A solution of the protected guanidine from Example 3 (0.0624 g, 0.2 mmol) in 4N HCl was stirred at rt for 24 hr. The reaction was concentrated *in vacuo*. The residue was purified on silica gel and eluted with CH_3CN/HOAc/H_2O 4/1/1. The product was a white glass and obtained in 25% yield: R_F 0.34 (CH_3CN/HOAc/H_2O 4/1/1); $[\alpha]_D^{20}$ = +17.48° (c=0.15, H_2O); ^1H NMR (300 MHz, D_2O) δ: 3.68 (dd, J=11.7, 6.6 Hz, 1H), 3.84 (dd, J=11.7, 4.5 Hz, 1H), 3.92 (bd, J=4.5 Hz, 2H), 3.95 (m, 1H), 5.73 (dd, J=15.5, 7.5 Hz, 1H), 5.98 (dt, J=15.5, 4.5 Hz, 1H); MS(DCI/NH_3) *m/e* 159 ($m+H^+$); Analysis calc'd for $C_6H_{14}N_4O$ • 2.0 HCl • 0.7 H_2O: C 29.57; H 7.20; N 22.99. Found: C 29.82; H 7.06; N 22.86.

Example 5

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-aminoguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

The material from Example 1h (3-(1,1-dimethylethyl)-(S)-4-(3-aminopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate) (127 mg, 0.5 mmol) and TEA (153 µL, 1.1 mmol) were dissolved in 5 mL Et_2O and treated with cyanogen bromide (CNBr, 183 µL, 0.55 mmol, 3 M in CH_2Cl_2) in 1 portion. After 10 min, 5 mL EtOH and NH_2NH_2·HCl (35.9 mg, 0.55 mmol) were added. After 1 day, additional NH_2NH_2·HCl (36 mg) was added and the reaction mixture was heated at 80°C for 3 days. The cooled reaction mixture was chromatographed on silica gel, eluted with 5:2 EtOAc-PAW to provide diaminotriazole (by-product resulting from over cyanation, MW=338, 24 mg, 0.07 mmol, 14%) followed by desired product

110.6 mg, 0.35 mmol, 71% yield (cf. Wagenaar and Kerwin, *J. Org. Chem.* **1993**, 58: 4331-4338): $[\alpha]_D^{20}$ = +40.6° (c=0.17, $CDCl_3$); ^1H NMR (300 MHz, CD_3OD) δ: 1.42-1.53 (m, 12H), 1.55-1.58 (m, 3H), 3.52 (d, J=6 Hz, 0.5H), 3.73 (dt, J=2, 12 Hz, 1H), 3.83-3.86 (m, 1.5H), 4.05-4.12 (m, 1H), 4.37 (bs, 1H), 5.58-5.76 (m, 1.5H), 5.86 (ddt, J=15, 7, 1 Hz, 0.5H); MS(DCI) *m/e* 314(m+H)$^+$, 257, 158.

Example 6

N^G-Aminoguanidinyl-4(S)-amino-pent-2,E-ene-5-ol

The product of Example 5 (91 mg, 0.29 mmol) was treated with 3 mL 6N HCl for 2 hr and then the reaction mixture was diluted and lyophilized. The crude product was chromatographed on silica gel eluted with 1:2 EtOAc-PAW to provide 27.1 mg, 0.11 mmol, 38% yield: R_F 0.2 (1:2 EtOAc-PAW); 2 spots observed by tlc and confirmed by 2d-tlc.; $[\alpha]_D^{20}$ = +10.0° (c=0.08, CD_3OD); ^1H NMR (500 MHz, D_2O) δ: 3.66-3.73 (m, 2.3H), 3.81-3.85 (m, 1.7H), 3.92-4.03 (m, 3H), 5.68-5.74 (m, 0.7H), 5.92-6.05 (m, 1.3H); MS(DCI) *m/e* 174(m+H)$^+$, 134, 119, 117.

Example 7

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-hydroxyguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

The material from Example 1h (3-(1,1-dimethylethyl)-(S)-4-(3-aminopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate) (512 mg, 2 mmol) was dissolved in 20 mL of Et_2O and treated with CNBr (732 µL, 2.2 mmol, 3 M in CH_2Cl_2), followed by TEA (613 µL, 4.4 mmol). After 10 minutes, EtOH (20 mL) and NH_2OH·HCl (306 mg, 4.4 mmol) were added and the reaction was stirred overnight at rt (cf. Wagenaar and Kerwin, *J. Org. Chem.* **1993**, 58: 4331-4338). After evaporation of the solvent, chromatography of the residue and elution with 5:1 EtOAc-PAW resulted in 602 mg of product, 1.91 mmol, 96% yield: R_F 0.2 (5:1 EtOAc-PAW); ^1H NMR (300 MHz, CD_3OD) δ: 1.4-1.5 (m, 12H), 1.57 (s, 3H), 3.73 (dd, J=2, 9 Hz, 1H), 3.86 (d, J=4 Hz, 2H), 4.07 (dd, J=7, 9 Hz, 1H), 4.37 (bs, 1H), 5.58-5.78 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 23.6, 23.8, 25.0, 27.0, 27.6, 28.7, 43.0, 60.0, 69.0, 81.2, 81.9, 95.1, 127.3, 132.6, 133.5, 160.3; MS(DCI) *m/e* 315 (m+H)$^+$; MS(DCI) calc'd for $C_{14}H_{27}N_4O_4$: *m/e* 315.2032, found: 315.2020; $[\alpha]_D^{23}$ = +29.3° (c=1.1, MeOH).

Example 8

N^G-Hydroxyguanidinyl-4(S)-amino-pent-2,E-ene-5-ol

The product of Example 7 (19.6 mg, 0.062 mmol) was treated with 5 mL of 4N HCl in dioxane at 4°C and allowed to reach rt. After 1 hr, the reaction mixture was filtered and the resulting solid was rinsed with Et_2O. The hygroscopic solid was dissolved in H_2O and lyophilized to provide 11.4 mg, 83% yield: ^1H NMR (300 MHz, D_2O) δ: 3.69 (dd, J=7, 15 Hz, 1H), 3.76 (s, 2H), 3.84 (dd, J=4, 15 Hz, 1H), 3.94-4.03 (m, 3H), 5.72 (ddt, J=2, 7, 15 Hz, 1H), 5.98 (ddt, J=1, 6, 15 Hz, 1H); MS(DCI) *m/e* 175 $(m+H)^+$, 160, 117, 103, 80; HRMS(DCI) calc'd for $C_6H_{15}N_4O_2$: *m/e* 175.1195, found: 175.1190.

Example 9

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-methylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of 3-(1,1-dimethylethyl)-(S)-4-(3-aminopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 1h (0.2083 g) in EtOH/H_2O 1/1 (9 mL) was added N,S-dimethyl-pseudothiouronium sulfate salt (2.0 eq) and TEA (1.33 eq) and the reaction was stirred at rt for 24 hr. The mixture was concentrated *in vacuo*. The residue was purified on silica gel and eluted with CH_3CN/HOAc/H_2O 12/1/1. The material was a colorless oil and was obtained in 17%. : R_F 0.65 (CH_3CN/HOAc/H_2O 12/1/1); $[\alpha]_D^{20}$ = + 39.3 (c=0.21, MeOH); ^1H NMR (300 MHz, CD_3OD) δ: 1.47 (s, 9H), 1.51 (s, 3H), 1.60 (s, 3H), 2.83 (s, 3H), 3.57 (m, 2H), 3.60 (m, 1H), 3.82 (d, J=3.5 Hz, 1H), 4.08 (m, 1H), 5.70 (m, 2H); ^{13}C NMR (500 MHz, D_2O) δ: 161.5, 134.3, 126.8, 64.2, 56.7, 44.7, 44.5. MS(FAB/MAT90) *m/e* 313 $(m+H)^+$; Analysis calc'd for $C_{15}H_{28}N_4O_3$: C 57.66; H 9.03; N 17.93; Found: C 57.31; H 8.92; N 17.84.

Example 10

N^G-Methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol

To a solution of 3-(1,1-dimethylethyl)-(S)-4-(3-N^G-methylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 9 (0.0889 g) in CH_2Cl_2 (10 mL) at rt was added TFA (2.0 mL) and the reaction mixture was stirred at rt for 1 hr and concentrated *in vacuo*. The residue was purified on silica gel and eluted with CH_3CN/H_2O/HOAc 3/1/1. The product was a yellow oil/foam and was obtained in 61% yield: R_F 0.15 (CH_3CN/H_2O/HOAc 3/1/1); ^1H NMR (300 MHz,

CD_3OD) δ: 2.83 (s, 3H), 3.60 (m, 2H), 3.68 (m, 2H), 3.87 (d, J=6.5 Hz, 1H), 5.23 (dd, J=15.5, 6.0 Hz, 1H), 5.92 (dt, J=16.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 28.2, 43.3, 55.5, 63.2, 127.4, 132.4, 158.4; MS(FAB/MAT90) *m/e* 173 $(m+H)^+$; $[\alpha]_D^{20}$ = +26.20° (c=1.32, MeOH); Analysis calc'd for $C_7H_{16}N_4O$ • 3.0 TFA: C 30.36; H 3.72; N 10.89; Found: C 30.72; H 3.40; N 10.74.

Alternately, to a solution of 3-(1,1-dimethylethyl)-(S)-4-(3-N^G-methyl-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 9 (0.5784 g) in CH_2Cl_2 (15 mL) with 0.5 mL of CH_3OH was added TFA (2.0 eq) and the reaction mixture was stirred at rt for 1.5 hr under a N_2 atmosphere. The mixture was concentrated *in vacuo*. The residue was purified on amberlite CG-120 and eluted with 1.0 N HCl up to 4.5 N HCl. The material was a yellow oil and was obtained in 71%: R_F 0.30 (CH_3CN/HOAc/H_2O 3/1/1); ^1H NMR (300 MHz, D_2O) δ: 2.83 (s, 3H), 3.68 (dd, J=9, 15 Hz, 1H), 3.82 (dd, J=6, 14 Hz, 1H), 3.90 (d, J=4.5 Hz, 1H), 3.95 (m, 2H), 5.75 (m, 1H), 5.95 (dt, J=5, 14 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ: 30.4, 44.7, 56.8, 64.2, 126.7, 135.0, 159.3; MS(FAB/MAT90) *m/e* 173 ($m+H)^+$; $[\alpha]_D^{20}$ = +9.72° (c=1.65, H_2O); Analysis calc'd for $C_7H_{16}N_4O$ • 4.0 HCl: C 26.43; H 6.33; N 17.61; Found C 26.17; H 5.97; N 17.41.

Example 11

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-ethylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of 3-(1,1-dimethylethyl)-(S)-4-(3-aminopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 1h (0.4293 g) in EtOH/H_2O 1/1 (6 mL) was added N-ethylamidine-2-sulfonic acid (0.2804 g, 1.1 eq) and K_2CO_3 (0.2548 g, 1.1eq) and the reaction was stirred at rt for 24 hr. The reaction mixture pH was adjusted to 12-14 and extracted with CH_2Cl_2 and concentrated *in vacuo*. The residue was purified on silica gel and eluted with CH_3CN/H_2O/HOAc 12/1/1. The material was a yellow oil and obtained in 82% yield.: R_F 0.40 (CH_3CN/HOAc/H_2O 12/1/1); $[\alpha]_D^{20}$ = + 18.0 (c=0.10, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.18 (t, J=9 Hz, 3H), 1.48 (s, 9H), 1.51 (s, 3H), 1.58 (s, 3H), 3.15 (m, 2H), 3.72 (m, 2H), 4.05 (dd, J=8, 16 Hz, 1H), 4.35 (m, 2H), 5.67 (m, 2H); MS(FAB/MAT90) *m/e* 327 $(m+H)^+$; Analysis calc'd for $C_{16}H_{30}N_4O_3$ • 0.5 HOAc: C 57.28; H 9.04; N 15.71; Found: C 57.39; H 9.04; N 16.00.

Example 12

N^G-Ethylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol

To a solution of 3-(1,1-dimethylethyl)-(S)-4-(3-N^G-ethylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 11 (0.57 g) in CH_2Cl_2 (15 mL) was added TFA (0.267 g, 2.0 eq) and 0.5 mL of H_2O. The reaction mixture was stirred at rt for 2-3 hr. The reaction was concentrated *in vacuo*. The residue was purified on silica gel and eluted with $CH_3CN/H_2O/HOAc$ 3/1/1. The product was a brown oil and obtained in 26% yield: R_F 0.30 ($CH_3CN/H_2O/HOAc$ 3/1/1); $[\alpha]_D^{20}$ = +21.26° (c=0.80, H_2O). ^1H NMR (300 MHz, CD_3OD) δ: 1.23 (t, J=9 Hz, 3H), 3.24 (m, 2H), 3.57 (m, 3H), 3.71 (dd, J=5, 11 Hz, 1H), 3.85 (d, J= 4.7 Hz, 1H), 5.72 (dt, J=10, 16 Hz, 1H), 5.90 (dt, J=9, 15.5 Hz, 1H); MS(FAB/MAT90) *m/e* 187 $(m+H)^+$; Analysis calc'd for $C_8H_{18}N_4O$: C 51.58; H 9.74; N 30.08; Found: C 47.17; H 8.50; N 16.14.

Example 13

N^4-Boc-N^G-Nitroguanidinyl-4(S)-amino-pent-2,E-ene-5-ol

To a solution of the guanidine from Example 2 (2.02 g, 12.0 mmol) at ambient temperature under a N_2 atmosphere was added TEA (2.43 g, 2 eq) and di-t-butyl-dicarbonate (3.929 g, 1.5 eq). The solution was stirred at ambient temperature for 4 hr following by tlc. The reaction was extracted with EtOAc and the combined organic extracts washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography eluting with CH_2Cl_2/MeOH (2:1) afforded the product as a colorless oil (51%): R_F 0.20 (2:1 CH_2Cl_2:MeOH); MS(DCI) *m/e* 259 $(m+H)^+$.

Example 14

3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

Step 14a. 3-(1,1-Dimethylethyl)-(S)-4-(3-(2-methyl-ethoxypropen-2E-oyl))-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the aldehyde from Example 1c (0.389 g, 1.70 mmoles) in THF (50 mL) at rt under a N_2 atmosphere was added (carbethoxy-ethylidene)triphenyl-phosphorane (0.696 g, 2.0 mmoles) and the reaction was stirred at rt for 24 hr. The reaction was concentrated *in vacuo* and the material was taken up in hexane and the triphenyl phosphine oxide was filtered off and concentrated *in vacuo* once again to give a yellow oil. The material was purified via flash chromatography with hexane/EtOAc 1/1. This resulted in a 84% yield of a

colorless oil.: R_F 0.70 (hexane/EtOAc 1/1); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.30 (t, J=7 Hz, 3H), 1.42 (s, 9H), 1.49 (s, 3H), 1.57 (s, 3H), 1.65 (s, 3H), 1.90 (d, J=12 Hz, 2H), 3.70 (dd, J= 6, 11 Hz, 1H), 4.12 (m, 1H), 4.21 (m, 2H), 4.60 (m, 1H), 6.65 (m, 1H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 12.5, 14.2, 24.4, 25.0, 26.4, 27.3, 28.3, 55.4, 60.6, 67.8, 140.4, 167.6; MS(DCI/NH_3) *m/e* 314 $(m+H)^+$, 331 $(m+NH_4)^+$; Analysis calc'd for $C_{16}H_{27}NO_5$: C 61.32; H 8.68; N 4.46; found: C 61.53; H 8.85; N 4.32.

Step 14b. 3-(1,1-Dimethylethyl)-(S)-4-(3-hydroxy-2-methylpropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate.

To a solution of the enoate from step 14a (0.1878 g, 0.60 mmoles) in ϕCH_3 (65 mL) cooled to -78°C under a N_2 atmosphere was added 1.0 M DIBAL (3.1 mL, 3.10 mmoles) over a 10 minute period while maintaining the temperature below -70°C. The reaction was stirred at -78°C for 1.5 hr and quenched with MeOH. The reaction was poured into 1M Rochelle salt and stirred for 30 minutes and allowed to separate. The organic layer was poured off, washed with brine and dried over Na_2SO_4. The material was concentrated *in vacuo* and purified on SiO_2 with EtOAc/hexane 1/1. A 74% yield of colorless oil product was obtained.: R_F 0.40 (EtOAc/hexane 1/1); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.53 (s, 3H), 1.60 (s, 3H), 1.74 (s, 3H), 3.67 (dd, J=4.5, 10.25 Hz, 1H), 4.04 (s, 2H), 4.08 (dd, J= 7, 12 Hz, 1H), 4.62 (m, 1H), 5.48 (d, J= 9.5 Hz, 1H); MS(DCI/NH_3) *m/e* 272 $(m+H)^+$, 289 $(m+NH_4)^+$; Analysis calc'd for $C_{14}H_{25}NO_4$: C 61.96; H 9.28; N 5.16; found: C 62.18; H 9.36; N 5.08.

Step 14c. 3-(1,1-Dimethylethyl)-(S)-4-(3-phthalimido-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the mesylate (0.1047 g, 0.30 mmoles) (prepared from the alcohol in step 14b in a manner consistent with step 1f) in DMF (20 mL) under a N_2 atmosphere was added potassium phthalimide (0.2038 g, 1.10 mmoles) and the reaction was warmed to 80°C for 12 hr. The reaction was poured into EtOAc and washed with H_2O (50 mL) and brine (30 mL) and dried over $NaSO_4$. The organic extract was concentrated *in vacuo* and purified on SiO_2 with hexane/EtOAc 1/1. The product was a colorless oil and was obtained in 69% yield: R_F 0.60 (EtOAc/hexane 1/1); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.42 (s, 9H), 1.51 (s, 3H), 1.58 (s, 3H), 1.73 (s, 3H), 3.65 (dd, J=6, 12 Hz, 1H), 4.02 (m, 1H), 4.22 (m, 2H), 4.55 (m, 1H), 5.42 (bs, 1H), 7.73 (m, 2H), 7.86 (m, 2H); MS(FAB) *m/e* 401 $(m+H)^+$; Analysis calc'd for $C_{22}H_{28}N_2O_5$: C 65.98; H 7.04; N 6.99; found: C 65.77; H 6.87; N 6.80.

Step 14d. 3-(1,1-Dimethylethyl)-(S)-4-(3-amino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate.

To a solution of the phthalimide from step 14c (0.0400 g, 0.10 mmoles) in MeOH (4.0 mL) at rt under a N_2 atmosphere was added 85% N_2H_4 and the reaction mixture was warmed to 40°C for 24 hr. The reaction was then poured into brine and washed (3x) with 25 mL of CH_2Cl_2, dried over Na_2SO_4, and concentrated *in vacuo*. The material was purified on SiO_2 with EtOAc/hexane 1/1. The product was a white solid and was obtained in 81% yield: R_F 0.30 (EtOAc/hexane 1/1); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.52 (s, 3H), 1.61 (s, 3H), 1.75 (s, 3H), 3.22 (s, 2H), 3.65 (dd, J=4.5, 9 Hz, 1H), 4.05 (dd, J=7, 13 Hz, 1H), 4.60 (m, 1H), 5.36 (d, J= 9.5 Hz, 1H); MS(FAB/MAT) *m/e* 271 $(m + H)^+$; Analysis calc'd for $C_{14}H_{26}N_2O_3$: C 62.19; H 9.67; N 10.36; found: C 61.87; H 9.40; N 10.09.

Step 14e. 3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate.

To a solution of the amine (0.1258 g) from example 14d in EtOH/H_2O 1/1 6 mL was added the N-nitro-S-methylthiouronium salt (0.0743 g, 1.0 eq), TEA (0.0743 g, 1.0 eq) and the reaction was stirred at rt for 24 hr. The reaction mixture was concentrated *in vacuo* . The residue was purified on SiO_2 and eluted with CH_3CN/HOAc/H_2O 12/1/1. The material was a colorless oil obtained in 47% yield: R_F 0.60 (CH_3CN/HOAc/H_2O 12/1/1); ^1H NMR(300 MHz, CD_3OD) δ: 1.45 (s, 9H), 1.54 (s, 3H), 1.59 (s, 3H), 1.75 (s, 3H), 3.63 (dd, J=2, 11.1 Hz, 1H), 3.71 (s, 2H), 4.10 (dd, J= 4.5, 15 Hz, 1H), 4.65 (m, 1H), 5.40 (m, 1H); MS(FAB/MAT90) *m/e* 358 $(m + H)^+$; $[\alpha]_D^{20}$ = +49.62° (c=1.0, MeOH); Analysis calc'd for $C_{15}H_{27}N_5O_5 \cdot 0.10$ HOAc: Calc: C 50.24; H 7.60; N 19.27; Found: C 49.90; H 7.99; N 19.00.

Example 15

N^G-Nitroguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol

Utilizing 3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 14e and the procedure described in Example 2, the title compound was prepared. To a solution of 3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 14e in a solution of CH_2Cl_2 (8.0 mL) under a N_2 atmosphere was added TFA (2.0 eq) and the reaction mixture was stirred at rt for 2 hr. The mixture was concentrated *in vacuo*. The residue was purified on silica gel and eluted with CH_3CN/HOAc/H_2O 3/1/1. The material was a yellow oil and was obtained in 46%: R_F 0.60 (CH_3CN/H_2O/HOAc 3/1/1); $[\alpha]_D^{20}$ = +25.0 (c=0.10, MeOH). ^1H NMR (300 MHz, D_2O) δ: 1.80 (s, 3H),

3.65 (dd, J=9, 14.5 Hz, 1H), 3.75 (dd, J=5, 12 Hz, 1H), 3.92 (s, 2H), 4.25 (m, 1H), 5.32 (d, J=9 Hz, 1H); MS(FAB/MAT95) *m/e* 218 $(m+H)^+$.

Example 16

3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

Step 16a. 3-(1,1-Dimethylethyl)-(S)-4-(3-(2-benzyl-benzyloxypropen-2E-oyl))-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the aldehyde from step 1c (0.3435 g, 1.50 mmoles) in THF (75 mL) at rt was added (carbobenzyloxy-benzylmethylidene) triphenylphosphorane (0.7776 g, 1.60 mmoles) and the reaction was stirred at rt for 24 hr under a N_2 atmosphere. The reaction was not complete after 24 hr, 1.6 mmoles of the phosphorane was added and the reaction was stirred for an additional 72 hr. The reaction was then concentrated *in vacuo* to give a yellow oily solid. The reaction mixture was solubilized in hexane and the triphenyl phosphine was removed by filtration. The reaction was purified on SiO_2 and eluted with EtOAc/hexane 1/1. The reaction produced a yellow oil in 27% yield: R_F 0.75 (EtOAc /hexane 1/1); $[\alpha]_D^{20}$ = +29.42 (c=0.65, MeOH). ^1H NMR(300 MHz, $CDCl_3$) δ: 1.38 (s, 9H), 1.48 (s, 3H), 1.54 (s, 3H), 2.69 (t, J= 7 Hz, 2H), 2.98 (t, J= 7.5 Hz, 2H), 3.57 (dd, J=4, 9.75 Hz, 1H), 3.82 (dd, J=7, 12 Hz, 1H), 5.15 (m, 2H), 7.25 (m, 10H); MS(FAB/MAT90) *m/e* 452 $(m+H)^+$; Analysis calc'd for $C_{27}H_{33}NO_5$: C 71.81; H 7.36; N 3.10; found: C 71.52; H 7.25; N 2.87.

Step 16b. 3-(1,1-Dimethylethyl)-(S)-4-(3-hydroxy-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate.

To a solution of the enoate from step 16a (0.2255 g, 0.50 mmoles) in ϕCH_3 (25 mL) cooled to -78°C under N_2 atmosphere was added DIBAL (1M in ϕCH_3) over a 10 minute period. The reaction was stirred at -78°C for 2 hr and quenched with MeOH. The reaction mixture was poured into 1M Rochelle salt and stirred for 30 minutes and allowed to separate. The organic layer was poured off and washed with brine and dried over $NaSO_4$. The solvent was evaporated to yield a yellow oil. The residue was purified on SiO_2 and eluted with EtOAc/hexane 1/1 which gave a 62% yield of a colorless oil: R_F 0.55 (EtOAc/hexane 1/1); $[\alpha]_D^{20}$ = +51.68 (c=1.28, CH_2Cl_2); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.48 (s, 3H), 1.61 (s, 3H), 3.58 (s, 2H), 4.01 (s, 2H), 4.34 (dd, J= 4.5, 8 Hz, 1H), 4.45 (dd, J= 5, 9 Hz, 1H), 4.62 (bs, 1H), 5.60 (d, J= 9.25 Hz, 1H), 7.28 (m, 5H); MS(DCI/NH_3) *m/e* 348

$(m+H)^+$, 365 $(m+NH_4)^+$; Analysis calc'd for $C_{20}H_{29}NO_4$: C 69.13; H 8.41; N 4.03; found: C 68.90; H 8.24; N 4.35.

Step 16c. 3-(1,1-Dimethylethyl)-(S)-4-(3-phthalimido-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate.

To a solution of the mesylate (prepared from the alcohol in step 16b by a manner similar to step 1f) (0.085 g, 0.20 mmoles) in DMF (10mL) was added the potassium phthalimide and the reaction was heated at 80°C for 24 hr under a N_2 atmosphere. The mixture was poured into CH_2Cl_2 and washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The material was purified on SiO_2 and eluted with EtOAc/hexane 1/1 to give a 57% yield of a colorless oil: R_F 0.70 (EtOAc/hexane 1/1); $[\alpha]_D^{20}$ = +21.26 (c=0.41, MeOH); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.41 (s, 9H), 1.50 (s, 3H), 1.58 (s, 3H), 3.75 (m, 1H), 4.01 (dd, J= 7, 15.5 Hz, 1H), 4.23 (m, 2H), 4.63 (bs, 1H), 4.86 (s, 2H), 5.66 (d, J= 9.5 Hz, 1H), 7.30 (m, 3H), 7.95 (m, 2H), 7.71 (m, 2H), 7.87 (m, 2H); MS(FAB/MAT90) *m/e* 477 $(m+H)^+$; Analysis calc'd for $C_{28}H_{32}N_2O_5$: C 70.56; H 6.76; N 5.87; found: C 70.37; H 6.42; N 5.78.

Step 16d. 3-(1,1-Dimethylethyl)-(S)-4-(3-amino-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate.

To a solution of the phthalimide from step 16c (0.0476 g, 0.10 mmoles) in MeOH (15 mL) was added 85% N_2H_4 and the reaction was warmed to 40°C for 24 hr under a N_2 atmosphere. The reaction was poured into brine (100 mL) and extracted with Et_2O (4x, 50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The material was purified on SiO_2 and eluted with MeOH containing 2% NH_4OH. This gave a 67% yield of a colorless oil. R_F=0.50 (MeOH with 2% NH_4OH); $[\alpha]_D^{20}$ = +41.82 (c=1.26, MeOH); ^1H NMR(300 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.51 (s, 3H), 1.63 (s, 3H), 3.20 (s, 2H), 3.68 (dd, J=4.5, 12.3 Hz, 1H), 3.77 (d, J=15 Hz, 2H), 3.98 (m, 1H), 4.71 (bs, 1H), 5.58 (d, J=10 Hz, 1H), 7.18 (m, 3H), 7.28 (m, 2H); MS(FAB/MAT90) *m/e* 347 $(m+H)^+$. Analysis calc'd for $C_{20}H_{30}N_2O_3 \cdot 0.3$ MeOH: C 68.47; H 8.83; N 7.86; Found: C 68.11; H 8.44; N 7.43.

Step 16e. 3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate.

Using the method of example 1i and the product of example 16d as starting material the product is prepared.

Example 17

N^4-Boc-N^G-Methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol

To a solution of 3-(1,1-dimethylethyl)-(S)-4-(3-aminopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 1h (0.257 g, 1.0 mmol) in EtOH/H_2O 1/1 (9.0 mL) was added N-methyl-S-methylthiopseudouronium sulfate (0.5560 g, 2.0 eq) and TEA (0.142 mmol, 1.0 eq) and the reaction mixture was stirred at rt for 24 hr. The reaction mixture was concentrated *in vacuo*. The residue was purified on silica gel and eluted with CH_3CN/HOAc/H_2O 12/1/1. In addition to the product N^G-Methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol (cf. Example 10) the title product was obtained in 12% yield as a white oil: R_F 0.50 (CH_3CN/HOAc/H_2O 12/1/1); ^1H NMR (300 MHz, CD_3OD) δ: 1.49 (s, 9H), 2.85 (s, 3H), 3.60 (m, 2H), 3.62 (m, 1H), 3.85 (d, J=3.8 Hz, 1H), 4.12 (m, 1H), 5.72 (m, 2H); MS(FAB/MAT90) *m/e* 273 $(m+H)^+$; Analysis calc'd for $C_{12}H_{24}N_4O_3 \cdot 1.0$ HOAc: Calc: C 50.58; H 8.49; N 16.85; Found: C 50.32; H 8.13; N 16.79.

Example 18

3-(1,1-Dimethylethyl)-(R)-4-(3-N^G-methylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

Utilizing 3-(1,1-dimethylethyl)-(R)-4-(3-aminopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate prepared in an analogous manner to its enantiomer from Example 1h and N,S-dimethyl-pseudothiouronium sulfate salt, the title compound is prepared using the procedure described in Example 1g. To a solution of 3-(1,1-dimethylethyl)-(R)-4-(3-aminopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate prepared in an analogous manner to its enantiomer from Example 1h (0.1965 g) in EtOH/H_2O (4/1) (1.0 M) was added N,S-dimethyl-pseudothiouronium sulfate salt (1.1 eq) and TEA (1.1 eq) and the reaction mixture was stirred at rt for 48 hr. The mixture was concentrated *in vacuo*. The residue was purified on silica gel and eluted with CH_3CN/HOAc/H_2O (12/1/1). The material was not pure so another silica gel column was run with elution with CH_2Cl_2/CH_3OH (3/1). The material was a colorless oil and obtained in 62% yield: R_F 0.70 (CH_3CN/HOAc/H_2O 12/1/1/1); $[\alpha]_D^{20} = -44.9$ (c=0.76, MeOH); ^1H NMR (300 MHz, CD_3OD) δ: 1.48 (s, 9H), 1.50 (s, 3H), 1.58 (s, 3H), 2.75 (s, 3H), 3.53 (m, 2H), 3.72 (dd, J= 5, 12 Hz, 1H), 3.85 (d, J= 4.5 Hz, 1H), 4.10 (dd, J= 7, 14.5 Hz, 1H), 5.65 (m, 2H); MS (FAB/MAT90) *m/e* 313 $(m+H)^+$; Analysis calc'd for $C_{15}H_{28}N_4O_3 \cdot 3.0$ CH_2Cl_2: C 38.11; H 6.04; N 9.87; Found: C 38.35; H 6.03; N 9.88.

Example 19

N^G-Methylguanidinyl-4(R)-amino-pent-2,E-ene-5-ol

To a solution of 3-(1,1-dimethylethyl)-(R)-4-(3-N^G-methylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 18 (2.0 mg) in CH_2Cl_2 was added 0.10 mL of TFA and one drop of H_2O. When the reaction did not appear to proceed by tlc 4N HCl (2 mL) was added. The reaction mixture was stirred for 1 hr and concentrated *in vacuo*. The material residue was purified over silica gel and eluted with CH_2Cl_2/MeOH (3/1) with 5% HOAc. Product yield was 18%: R_F 0.25 (CH_2Cl_2/MeOH (3/1, with 5% HOAc); ^1H NMR(300 MHz, CD_3OD) δ: 2.82 (s, 3H), 3.55 (m, 2H), 3.70 (m, 2H), 3.85 (d, J=7.5 Hz, 1H), 5.25 (m, 1H), 5.85 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 28.2, 43.3, 55.5, 63.2, 127.0, 132.4, 158.4; MS(FAB/MAT90) *m/e* 173 $(m+H)^+$; $[\alpha]_D^{20}$ = -12.62° (c=0.60, MeOH); Analysis calc'd for $C_7H_{16}N_4O$ • 3.2 HOAc: C 44.16; H 7.96; N 15.39; Found: C 43.92; H 7.68; N 15.16.

Example 20

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of 3-(1,1-Dimethylethyl)-(S)-4-(3-amino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from step 14d (0.1253 g) in EtOH/H_2O 1/1 10 mL was added N,S-dimethyl-pseudothiouronium sulfate salt (0.1355 g, 1.0 eq), TEA (0.0493 g, 1.0 eq) and the reaction was stirred at rt for 48 hr. The reaction was concentrated *in vacuo*. The product was purified on silica gel and eluted with CH_3CN/MeOH 1/1 with 0.5% HOAc. The material was a colorless oil and obtained in 64%: R_F 0.30 (CH_3CN/HOAc/H_2O 12/1/1); ^1H NMR(300 MHz, CD_3OD) δ: 1.46 (s, 9H), 1.50 (s, 3H), 1.57 (s, 3H), 1.75 (s, 3H), 3.63 (dd, J = 2.4, 8.7 Hz, 1H), 3.72 (s, 2H), 4.12 (dd, J= 6, 8.7 Hz, 1H), 4.65 (m, 1H), 5.40 (m, 1H); MS(FAB/MAT90) *m/e* 313 $(m+ H)^+$; $[\alpha]_D^{20}$ = +62.00° (c=1.00, MeOH); Analysis calc'd for $C_{15}H_{28}N_4O_3$ • 0.10 HOAc: C 51.78; H 8.26; N 11.95; Found: C 51.38; H 8.50; N 11.99.

Example 21

N^G-Guanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol

To a solution of 3-(1,1-Dimethylethyl)-(S)-4-(3-guanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from Example 20 (.0698 g) in CH_2Cl_2

10 mL was added 5.0 mL of TFA and 0.10 mL of H_2O. The reaction was stirred at rt for 1.5 hr. The reaction was concentrated *in vacuo*. The residue was purified on silica gel and eluted with CH_3CN/HOAc/H_2O 3/1/1. The product was a white solid and obtained in 84% yield: R_F 0.20 (CH_3CN/HOAc/H_2O 3/1/1); ^1H NMR(300 MHz, D_2O) δ: 1.78 (s, 3H), 3.62 (dd J= 5.5, 9 Hz, 1H), 3.72 (dd, J= 5, 8 Hz, 1H), 3.83 (s, 2H), 4.25 (m, 1H), 5.28 (dq, J= 3, 9.5 Hz, 1H); MS(FAB/MAT90) *m/e* 173 $(m+H)^+$; $[\alpha]_D^{20}$ = +12.26° (c=1.00, H_2O); Analysis calc'd for $C_7H_{16}N_4O$ • 3.20 HOAc • 0.90 H_2O: C 42.29; H 8.10; N 14.72; Found: C 42.27; H 7.90; N 14.63.

Example 22

3-(1,1-Dimethylethyl)-(R)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

Utilizing the same procedure outlined in example 3 the enantiomer of example 3 is prepared: To a solution of the enantiomeric R-allylic amine (1.0 eq) in EtOH/H_2O 1/1 was added the S-methyl-pseudothiouronium sulfate (1.0 eq) and TEA (1.0 eq) and the reaction was stirred at rt for 24 hr. The reaction was concentrated *in vacuo*. The residue was purified on silica gel and eluted with CH_3CN/MeOH (1/1 with 1% HOAc): R_F 0.35 CH_3CN/MeOH (1/1 with 1% HOAc); ^1H NMR(300 MHz, CD_3OD) δ: 1.49 (bs, 12H), 1.56 (s, 3H), 3.73 (dd, J= 1.8, 11.4 Hz, 1H), 3.82 (d, J=3.6 Hz, 2H), 4.08 (dd, J=5.7, 11.4 Hz, 1H), 4.37 (m, 1H), 5.66 (m, 2H); ^{13}C NMR(75 MHz, CD_3OD) δ: 23.8, 25.0, 27.0, 27.7, 28.7, 43.1, 59.95, 69.0, 81.95, 95.1, 132.6, 133.5, 158.9; HRMS(DCI/NH_3) calc'd for $C_{14}H_{27}N_4O_3$: *m/e* 299.2083, found: 299.2071; $[\alpha]_D^{20}$ = - 24.95° (c=1.1, MeOH); Analysis calc'd for $C_{14}H_{26}N_4O_3$ • 1.40 H_2O • 3.3 HOAc • 1.5 CH_3CN: C 48.59; H 8.03; N 13.21; Found: C 48.55; H 7.72; N 13.16.

Example 23

1-Guanidinyl-4(R)-amino-pent-2,E-ene-5-ol

Utilizing the material from example 22 and the procedure of example 4 the product is prepared.

Example 24

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidino-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate.

To a solution of 3-(1,1-Dimethylethyl)-(S)-4-(3-amino-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from example 16d (0.0622 g) in EtOH/H_2O 1/1 (4mL) was added S-methyl-pseudothiouronium sulfate salt (0.050 g, 1.1 eq) and TEA (0.0364 g, 2.0 eq) and the reaction was stirred at rt for 72 hr. The reaction was concentrated *in vacuo*. The material was purified on silica gel and eluted with CH_2Cl_2/MeOH/HOAc, (49/49/0.5). The product was a yellow oil obtained in 26% yield: R_F 0.30 (CH_2Cl_2/MeOH/HOAc (49/49/0.5); $[\alpha]_D^{20}$ = + 26.42° (c=0.16, MeOH); ^1H NMR(300 MHz, CD_3OD) δ: 1.50 (s, 9H), 1.58 (s, 3H), 1.62 (s, 3H), 3.35 (s, 2H), 3.62 (m, 1H), 4.25 (m, 4H), 4.72 (bs, 1H), 5.63 (m, 1H), 7.25 (m, 5H); MS(FAB/MAT90) *m/e* 389 $(m+H)^+$; Analysis calc'd for $C_{21}H_{32}N_4O_3 \cdot 3.0$ HOAc: C 57.02; H 7.79; N 9.85; Found: C 57.24; H 7.68; N 9.87.

Example 25

N^G-Guanidinyl-4(S)-amino-2-benzyl-pent-2,E-ene-5-ol

To a solution of the material from example 24 (0.0078 g) in CH_2Cl_2 (2.0 mL) under a N_2 atmosphere was added TFA (2 mL) and one drop of H_2O and the reaction was stirred at rt for 1.5 hr. The mixture was concentrated and purified on silica gel and eluted with CH_3CN/HOAc/H_2O 3/1/1. The material was further purified on CG-120 amberlite and eluted with 1.0N HCl up to 4.0N HCl. The product was a yellow oil and obtained in 12% yield: R_F 0.30 (CH_3CN/H_2O/HOAc, 3/1/1); $[\alpha]_D^{20}$ = +16.2 (c=0.18, H_2O). ^1H NMR (300 MHz, D_2O) δ: 3.60 (s, 2H), 3.65 (m, 1H), 3.75 (m, 1H), 3.82 (s, 2H), 4.00 (m, 1H), 5.65 (dd, 1H, J=15.0 Hz), 7.35 (m, 5H); MS(FAB/MAT95) *m/e* 249 $(m+H)^+$; Analysis calc'd for $C_{13}H_{20}N_4O \cdot 6.0$ HCl: C 33.42; H 5.61; N 11.99; Found: C 33.22; H 5.96; N 11.70.

Example 26

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-methylguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

Utilizing the material 3-(1,1-Dimethylethyl)-(S)-4-(3-amino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from example 14d and the procedure from example 9 the title compound is prepared. R_F 0.30 (CH_3CN/H_2O/HOAc 12/1/1); $[\alpha]_D^{20}$ = +6.81 (c=0.21, MeOH); ^1H NMR (300 MHz, CD_3OD) δ: 1.48 (s, 9H), 1.50 (s, 3H), 1.56 (s, 3H), 1.92 (s, 3H), 2.85 (s, 3H), 3.52 (m, 1H), 3.75 (s,

2H), 4.10 (dd, J=4, 9 Hz, 1H), 4.40 (m, 1H), 5.35 (d, J= 8.5 Hz, 1H); MS(FAB) *m/e* 327 $(m+H)^+$.

Example 27

N^G-Methylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol

To a solution of the material from example 26 (0.010 g) in CH_2Cl_2 (2.0 mL) under a N_2 atmosphere was added TFA (2 mL) and the reaction mixture was stirred at rt for 2 hr. The mixture was concentrated *in vacuo*. The residue was purified on ion-exchange CG-120 amberlite and eluted with 1N HCl up to 6N HCl. The material was a yellow oil and obtained in 21% yield: R_F 0.35 ($CH_3CN/HOAc/H_2O$, 3/1/1); ^1H NMR (300 MHz, D_2O) δ: 1.80 (s, 3H), 2.87 (s, 3H), 3.67 (dd, J=5.25, 15 Hz, 1H), 4.04 (s, 2H), 4.12 (dd, J=4, 11.5 Hz, 1H), 4.70 (m, 1H), 5.52 (d, J= 4.2 Hz, 1H); MS(FAB/MAT95) *m/e* 187 $(m+H)^+$; $[\alpha]_D^{20}$ = +7.28° (c=0.24, H_2O); Analysis calc'd for $C_8H_{18}N_4O \cdot 7.0$ HCl: C 21.76; H 5.57; N 12.69; Found C 21.46; H 5.37; N 12.37.

Example 28

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-propylguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of 3-(1,1-Dimethylethyl)-(S)-4-(3-amino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate from example 14d (0.1219 g) in $EtOH/H_2O$ (1/1) (10 mL) was added N-propyl-S-methyl-pseudothiouronium hydrochloride salt (1.1eq) and then K_2CO_3 (1.1eq). The reaction was stirred at rt for 48 hr. The reaction was concentrated *in vacuo*. The product was purified on silica gel and eluted with $CH_3CN/HOAc/H_2O$ (12/1/1). The product was a colorless oil and obtained in 21% yield: R_F 0.50 ($CH_3CN/HOAc/H_2O$, 12/1/1); $[\alpha]_D^{20}$ = + 31.6 (c=0.28, MeOH); ^1H NMR (300 MHz, CD_3OD) δ: 0.95 (t, J=9.5 Hz, 3H), 1.48 (s, 9H), 1.51 (s, 3H), 1.58 (s, 3H), 1.62 (m, 2H), 1.75 (s, 3H), 3.17 (t, J=11.5 Hz, 2H), 3.62 (dd, J=6, 12 Hz, 1H), 3.75 (bs, 2H), 4.11 (dd, J=6.5, 12 Hz, 1H), 4.68 (m, 1H), 5.36 (bs, 1H); MS(FAB/MAT95) *m/e* 355 $(m+H)^+$; Analysis calc'd for $C_{18}H_{34}N_4O_3$: C 60.98; H 9.66; N 15.80; Found C 60.59; H 9.42; N 15:33.

Example 29

N^G-Propylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol

Utilizing the material from example 28 and the procedure from example 4 the title compound is prepared.

Example 30

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-nitroguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

Step 30a. N-[(1,1-Dimethylethoxy)carbonyl]-D-serine methyl ester

To a solution of D-Boc-serine (5.13 g, 25 mmol) in EtOH cooled to 0°C was added diazomethane (4-5 eq) in a solution of Et_2O. After the addition of the diazomethane, the reaction was stirred for one hour and then quenched with glacial HOAc. The product was extracted with EtOAc. The combined organic extracts were washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography eluting with hexane/EtOAc (1:1) afforded the product (72%) as a yellow liquid: R_F 0.75 (EtOAc:hexane 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 2.48 (s, 1H), 3.82 (s, 3H), 3.90 (dd, J=4, 12 Hz, 1H), 3.95 (dd, J=4, 12 Hz, 1H), 4.40 (m, H), 5.45 (m, H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2, 52.5, 55.6, 60.4, 63.2, 80.2, 155.7, 171.4; MS(DCI/NH_3) *m/e* 220 $(m+H)^+$, 237 $(m+NH_4)^+$. Analysis calc'd for $C_9H_{17}NO_5 \cdot 0.5\ H_2O$: C 47.36; H 7.95; N 6.14. Found: C 47.20; H 7.58; N 6.12.

Step 30b. 3-(1,1-Dimethylethyl) 4-methyl-(R)-2,2-dimethyl-3,4-oxazolidinecarboxylate

To a solution of the methyl ester of Example 30a (1.05 g, 4.8 mmol) in benzene was added 2-methoxypropane (1.0 g, 2 eq) and p-TsOH (0.0914 g, 0.1 eq), and the reaction mixture was heated to reflux for 48 hr. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed with brine and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography eluting with EtOAc and hexane afforded the product as a yellow liquid in 78% yield: R_F 0.5 (1:1 hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 1.55 (br s, 3H), 1.64 (s, 3H), 3.80 (s, 3H), 4.25 (m, 1H), 4.38 (dd, J=6, 9Hz, 1H), 4.50 (dd, J=6, 8.5 Hz, 1H); MS(DCI/NH_3) *m/e* 260 $(m+H)^+$, 277 $(m+NH_4)^+$, 221 $(m-C_4H_9)$. Analysis calc'd for $C_{12}H_{21}NO_5 \cdot 0.75\ CH_2Cl_2$: C 47.41; H 7.02; N 4.34. Found: C 46.86; H 6.67; N 4.29.

Step 30c. 1,1-Dimethylethyl (R)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the methyl ester of Example 30b (4.61 g, 17.8 mmol) in ϕCH_3 cooled to -78°C was added 1 M DIBAL (2.2 mL, 2.2 eq) over a 15-20 minute period. The reaction mixture was stirred for 3-4 hr at -78°C and then quenched with CH_3OH at -78°C. The reaction mixture was extracted with EtOAc and the

combined organic extracts were washed with NaOH, H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the product as a colorless oil (64%): R_F 0.45 (1:1 EtOAc:hexane); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.49 (s, 9H), 1.52 (s, 3H), 1.58 (s, 3H), 3.80 (m, 1H), 4.20 (m, 2H), 4.40 (m, 1H), 9.53 (br s, 1H); MS(DCI/NH_3) *m/e* 230 $(m+H)^+$, 247 $(m+NH_4)^+$, 191 $(m-C_4H_9)$; $[\alpha]_D^{20°}$ = -24.72° (c=1.0, EtOH).

Step 30d. 3-(1,1-Dimethylethyl)-(S)-4-(3-(methoxypropen-2,Z-oyl))-2,2-dimethyl-3-oxazolidinecarboxylate

To a -78°C solution of anhydrous THF under a N_2 atmosphere was added 18-crown-6 (13.73 g, 2.0 eq) and the bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)-phosphonate (8.26 g, 1.0 eq) and the solution was stirred for 15 min. After 15 min the potassium bis(trimethylsilyl)amide (1.0 eq, 26 mL as an 0.5 M solution in ϕCH_3) was added and stirred for 10 min. A solution of aldehyde from Example 30c (5.95 g, 26 mmol, 1.0 eq) was added in 60 mL of THF over a 10 minute period and the reaction was stirred for 45 min. The reaction mixture was poured into H_2O and shaken. CH_2Cl_2 (300 mL) was added and shaken. The CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated *in vacuo*. The material was purified on neutral silica and eluted with EtOAc/hexane 1/1. This provided a 74% yield of the desired material (white solid): R_F 0.50 (EtOAc/hexane 1/1); $[\alpha]_D^{20°}$ = +33.21° (c=1.15, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.40 (s, 3H), 1.48 (s, 9H), 1.53 (s, 3H), 1.62 (s, 3H), 3.80 (dd, J=5, 9 Hz, 1H), 4.27 (m, 1H), 5.38 (t, J=7.5 Hz, 1H), 5.85 (d, J=6 Hz, 1H), 6.27 (m, 1H); MS(DCI/NH3) *m/e* 286 $(m+H)^+$, 303 $(m+NH_4)^+$; Analysis calc'd for $C_{14}H_{23}NO_5$: C 58.93, H 8.12, N 4.91; found: C 58.84, H 8.08, N 4.79.

Step 30e. 3-(1,1-Dimethylethyl)-(S)-4-(3-hydroxypropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a -78°C solution of anhydrous toluene under a N_2 atmosphere was added the methyl ester from Example 30d (11.90 mmol, 3.38 g) and the compound was stirred in ϕCH_3 until the reaction temperature was -78°C. 1 M DIBAL (65.2 mL) was added to the reaction via N_2 pressure and was added at a rate to maintain the internal reaction temperature below -68°C. The reaction mixture was stirred at -78°C for 1.5 hr, then the reaction was quenched with CH_3OH at -78°C, and then the reaction mixture was poured into 1M Rochelle salt solution and stirred for 40 min. The reaction mixture was allowed to settle and the organic layer was decanted off. The organic layer was diluted by 30% with EtOAc, washed with brine, and dried over Na_2SO_4. The solution was concentrated *in vacuo*. The product was purified over neutral silica gel and eluted with EtOAc/hexane 1/1.

The reaction resulted in a 79% yield of the desired material (colorless oil): R_F 0.30 (EtOAc/hexane 1/1); $[\alpha]_D^{20°}$ = -33.61° (c=0.83, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 1.49 (s, 3H), 1.56 (s, 3H), 3.70 (dd, J=5, 11 Hz, 1H), 4.05 (m, 2H), 4.45 (dt, J=6, 9 Hz, 1H), 4.95 (m, 1H), 5.54 (t, J=12 Hz, 1H), 5.87 (m, 1H); MS(DCI/NH3) *m/e* 258 $(m+H)^+$, 275 $(m+NH_4)^+$; Analysis calc'd for $C_{13}H_{23}NO_4$: C 60.68, H 9.01, N 5.44; found: C 60.30, H 8.96, N 5.31.

Step 30f. 3-(1,1-Dimethylethyl)-(S)-4-(3-mesyloxypropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the alcohol from Example 30e (0.7395 g, 27 mmol) in CH_2Cl_2 (1.0 M) at 0°C under a N_2 atmosphere was added TEA (0.4402 g, 1.5 eq) and MsCl (0.3936 g, 1.1eq) and the reaction was allowed to warm to rt and stirred for 1 hour. The reaction was poured into CH_2Cl_2 and washed with cold H_2O, 1N HCl, $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The reaction produced a quantitative yield of the desired material, yellow oil): R_F 0.70, (EtOAc/hexane 1/1); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 1.51 (s, 3H), 1.57 (s, 3H), 1.65 (s, 3H), 3.72 (dd, J=6, 12 Hz, 1H), 4.08 (m, 1H), 4.92 (m, 2H), 5.73 (m, 2H); MS(DCI/NH_3) *m/e* 336 $(m+H)^+$.

Step 30g. 3-(1,1-Dimethylethyl)-(S)-4-(3-phthalimidopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the mesylate from Example 30f (0.9729 g, 2.90 mmol) in anhydrous DMF (1.0 M) under a N_2 atmosphere at rt was added potassium phthalimide (0.6715 g, 3.6 mmol) and the reaction was heated at 80°C for 16 hr. The reaction was poured into EtOAc and washed with H_2O, brine and dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The material was purified on neutral silica, eluting with EtOAc/hexane 1/1. The product was a white solid and was obtained in 83%: R_F 0.80, (EtOAc/hexane 1/1); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.48 (s, 9H), 1.55 (s, 3H), 1.61 (s, 3H), 3.62 (dd, J=5, 9 Hz, 1H), 4.22 (t, J= 7 Hz, 2H), 4.60 (m, 1H), 5.00 (m, 1H), 5.63 (m, 1H), 7.71 (dd, J=4, 6 Hz, 2H), 7.85 (dd, J=4, 6 Hz, 2H); MS(DCI/NH_3) *m/e* 387 $(m+H)^+$, 404 $(m+NH_4)^+$; Analysis calc'd for $C_{21}H_{26}N_2O_5$: C 64.27, H 6.78, N 7.25; found: C 64.48, H 6.64, N 7.00.

Step 30h. 3-(1,1-Dimethylethyl)-(S)-4-(3-aminopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the phthalimide from Example 30g (0.3368 g, 0.90 mmol) in CH_3OH under a N_2 atmosphere was added N_2H_4 (0.1154 g, 4.0 eq) and the reaction mixture was stirred and heated to 40°C for 24 h. The mixture was cooled to rt and poured into EtOAc, washed with H_2O, brine and dried over Na_2SO_4. The material was purified on neutral silica gel, eluting with

$CH_2Cl_2/CH_3OH/NH_4OH$ 80/20/1. The product was a slightly yellow oil and was obtained in 79% yield: R_F 0.30 (CH_2Cl_2/EtOH/NH_4OH 80/20/1); $[\alpha]_D^{20°}$ = -57.00° (c=0.80, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ: 1.48 (s, 9H), 1.50 (s, 3H), 1.58 (s, 3H), 3.28 (m, 1H), 3.67 (dd, J=5, 9 Hz, 1H), 4.07 (dd, J=5, 9 Hz, 1H), 4.70 (m, 1H), 5.45 (t, J=12 Hz, 2H), 5.63 (m, 1H); MS(DCI/NH_3) *m/e* 257 $(m+H)^+$; Analysis calc'd for $C_{13}H_{24}N_2O_3 \cdot 0.10\ CH_2Cl_2$: C 59.41, H 9.21, N 10.57; found: C 59.27, H 9.30, N 10.67.

Step 30i. 3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-nitroguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the allylic amine of Example 30h (2.1 mmol, 0.5292 g) in EtOH/H_2O 1/1 was added N-nitro-S-methylthiouronium salt (0.2984 g, 2.6 mmol) and TEA (1.2 eq). The reaction was stirred for 3 hr before completion. The reaction was filtered and washed with cold CH_3OH. The solid was recrystallized from cold CH_3OH, (2x). The product was a white solid obtained in 87% yield: R_F 0.30 (CH_2Cl_2/EtOH/NH_4OH 95/5/1); $[\alpha]_D^{20°}$ = +86.07° (c=0.675, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.50 (s, 3H), 1.59 (s, 3H), 3.70 (dd, J= 5, 9 Hz, 1H), 4.05 (m, 1H), 4.10 (m, 1H), 4.40 (m, 1H), 4.64 (m, 1H), 5.50 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 24.5, 27.5, 28.5, 38.3, 54.0, 67.5, 81.3, 93.8, 128.75, 130.5, 152.9, 160.0; MS(DCI/NH_3) *m/e* 344 $(m+H)^+$; Analysis calc'd for $C_{14}H_{25}N_5O_5$: C 48.97, H 7.34, N 20.40; found: C 48.69, H 7.54, N 20.51.

Example 31

N^G-Nitroguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol

To a solution of the protected guanidino compound of Example 30i (0.3711 g, 1.1 mmol) was added a mixture of HCl/HOAc/H_2O 3/1/1 and the reaction was allowed to stir for 3 hr at rt. The reaction volume was diluted (2x) with H_2O and lyophilized. The material was purified on silica gel and eluted with CH_3CN/HOAc/H_2O 3/1/1. The material was a white solid and obtained in 94% yield: R_F 0.30 (CH_3CN/HOAc/H_2O 8/1/1); $[\alpha]_D^{20°}$ = +24.76° (c=0.735, H_2O). ^1H NMR (500 MHz, $CDCl_3$) δ: 3.75 (m, 2H), 3.90 (dd, J=9, 15 Hz, 1H), 4.10 (dd, J=9, 15 Hz, 1H), 4.35 (m, 1H), 5.62 (t, J=12 Hz, 1H), 5.95 (m, 1H); ^1H NMR (300 MHz, D_2O) δ: 3.79 (dd, J=7, 15 Hz, 1H), 3.71 (dd, J=7, 15 Hz, 1H), 3.95 (m, 1H), 4.10 (dd, J=3, 16 Hz, 1H), 4.35 (m, 1H), 5.63 (bt, J=15 Hz, 1H), 5.93 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 41.3, 52.9, 54.4, 127.5, 135.1, 162.1; MS (DCI/NH_3) 204 $(m+H)^+$; Analysis calc'd for $C_6H_{13}N_5O_3 \cdot 3.0$ HCl: C 21.09; H 4.95; N 20.49; found: C 21.16; H 5.18; N 20.47.

Example 32

N^4-t-Butyloxycarbonyl-4-amino-1-N^G-nitroguanidino-5-methoxy-(4,S)-2, Z-pentene

Step 32a. 2-Amino-5-phthalimido-(2,S)-3, Z-penten-1-ol hydrochloride

To the product of Example 30g (1.50 g, 3.88 mmol) was added 7.5 mL HOAc, 2.5 mL H_2O, and 0.5 mL 12M HCl. The mixture was allowed to stir at ambient temperature for approximately 3 hr, whereupon the volatile components were removed *in vacuo* to give the title compound as a white solid (1.10 g, 3.88 mmol) in quantitative yield. ^1H NMR (300 MHz, DMSO-d6) δ: 3.52 (m, 1H), 3.63 (m, 1H), 4.22 (m, 1H), 4.30 (d, J=7.5Hz, 2H), 5.49-5.58 (m, 2H), 5.78 (m, 1H), 7.82-7.91 (m, 4H), 8.16 (br s, 2H); MS(CI) *m/e* 247 $(m+H)^+$.

Step 32b. N^2-t-Butyloxycarbonyl-2-amino-5-phthalimido-(2,S)-3, Z-penten-1-ol

The product from Example 32a (501 mg, 1.77 mmol) was dissolved in 10 mL of anhydrous DMF. Di-t-butyl dicarbonate (464 mg, 2.12 mmol) and NMM (214 mg, 2.12 mmol) were added, and the reaction was allowed to stir at rt overnight whereupon the reaction was diluted with EtOAc and saturated aqueous $KHSO_4$. The layers were separated, and the organic layer was washed again with saturated aqueous $KHSO_4$, then with brine, dried with Na_2SO_4, filtered and the volatile components were removed *in vacuo* to give the title compound as a white solid (463 mg, 1.3 mmol) which was carried on without further purification. ^1H NMR (300 MHz, DMSO-d6) δ: 1.38 (s, 9H), 3.38 (m, 2H, partially obscured), 4.29 (t, J=7.5Hz, 1H), 4.38 (m, 1H), 4.74 (t, J=6Hz, 1H), 5.35-5.51 (m, 3H), 6.77 (m, 1H), 7.85 (m, 4H); MS (CI) *m/e* 364 $(m+NH_4)^+$, 347 $(m+H)^+$.

Step 32c. N^4-t-Butyloxycarbonyl-4-amino-5-methoxy-1-phthalimido-(4,S)-2, Z-pentene

The product of Example 32b (330 mg, 0.95 mmol) was dissolved in 4.75 mL of anhydrous DMF. Calcium sulfate ($CaSO_4$) (646 mg, 4.75 mmol), CH_3I (649 mg, 4.75 mmol), and freshly prepared silver (I) oxide (220mg, 0.95 mmol) were added, and the reaction was heated at 40-45°C for 72 h whereupon EtOAc was added. The organic layer was then washed twice with saturated aqueous $NaHCO_3$, twice with saturated aqueous $KHSO_4$, once with brine, dried over Na_2SO_4, filtered, and the the volatile components removed *in vacuo*. The resulting clear oil was subjected to silica gel chromatography eluting with hexane : acetone (3 : 1). The title compound was obtained as a white solid (227 mg, 0.63 mmol) contaminated with approximately 30% of the side product, N^4-(t-butoxycarbonyl-N-methyl)-4-amino-5-methoxy-1-phthalimido-(4,S)-2, Z-pentene.

The mixture was combined with material from a previous reaction and carried on without further purification. Removal of the side-product was effected during purification of the product from example 32d. ^{1}H NMR (300 MHz, $CDCl_3$) δ: Mixture of major and minor components: major component-1.45 (s, 9H), 3.38 (s, 3H), 3.47 (dd, J=6, 10.5 Hz, 1H), 3.55 (dd, J=6, 10.5 Hz, 1H), 4.37 (m, 1H), 4.57 (m, 1H), 4.82 (m, 1H), 5.02 (m, 1H), 5.60 (m, 2H), 7.70 (dd, J=3, 6Hz, 2H), 7.85 (dd, J=3, 6Hz, 2H). Partial Data- minor component 1.5 (s, 9H), 2.82 (s, 3H), 3.39 (s, 3H), 5.55 (m, 1H); MS (CI) major: *m/e* 378 $(m+NH_4)^+$, 361 $(m+H)^+$; minor: 392 $(m+NH_4)^+$, 375 $(m+H)^+$.

Step 32d. N^4-t-Butyloxycarbonyl-4-amino-1-N^G-nitroguanidino-5-methoxy-(4,S)-2, Z-pentene

The products from Example 32c (290 mg, 0.80 mmol) were dissolved in 4 mL of anhydrous CH_3OH and N_2H_4 hydrate (77 mg, 2.40 mmol) was added. The mixture was stirred at ambient temperature under nitrogen atmosphere overnight whereupon it was refluxed for 2 hr to effect phthaloyl deprotection. The volatile components were removed *in vacuo* and the resulting tan solids (190 mg) were dissolved in 2 mL of CH_3OH. TEA (97 mg, 0.96 mmol) and N-nitro-S-methylthiouronium salt (130 mg, 0.96 mmol) were added and the reaction mixture was stirred at ambient temperature under N_2 atmosphere overnight, whereupon the crude mixture was placed directly on silica gel, eluting with EtOAc : hexane : HOAc (30 : 20 : 2). Removal of the undesired N-methylated compound (obtained because of the mixture starting materials) was performed, fractions judged to be pure by tlc were pooled and the volatile components were removed *in vacuo* giving the title compound (89 mg, 0.28 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 3.34-3.40 (m, 4H, includes 3.37, s), 3.45 (dd, J=6, 10.5 Hz, 1H), 3.97 (dd, J=7.5, 18 Hz, 1H), 4.33-4.43 (m, 2H), 5.22 (d, J=7.5 Hz, 1H), 5.48-5.55 (m, 2H), 7.63 (br s, 2H), 8.58 (br s, 1H); MS(CI) *m/e* 335 $(m+NH_4)^+$, 318 $(m+H)^+$.

Example 33

4-Amino-1-N^G-nitroguanidino-5-methoxy-(4,S)-2, Z-pentene hydrochloride

The product of Example 32d was deprotected as in example 31. ^{1}H NMR (300 MHz, DMSO-d6) δ: 3.33 (s, 3H), 3.40-3.52 (m, 2H, partially obscured), 3.85-3.95 (br s, 2H), 4.31 (br s, 1H), 5.47 (t, J=12 Hz, 1H), 5.74 (m, 1H), 7.95-8.08 (br s, 2H), 8.10-8.20 (br s, 3H); MS(FAB$^+$) *m/e* 218 $(m+H)^+$; Analysis calc'd for $C_7H_{15}N_5O_3 \cdot 1.3\ HCl \cdot 0.1$ dioxane$\cdot 0.1\ Et_2O$: C 33.36; H 6.50; N 24.94; found: C 33.61; H 6.60; N 25.26.

Example 34

N^2-Methyl-N^2-t-butyloxycarbonyl-2, 5-diamino-1-t-butyldimethylsilyloxy-(2,S)-3,Z-pentene

Step 34a. N^2-t-Butyloxycarbonyl-2-amino-1-t-butyldimethylsilyloxy-5-phthalimido-(2,S)-3,Z-pentene

To the product of Example 32b (200 mg, 0.58 mmol) and freshly recrystallized imidazole (chloroform / hexane) dissolved in DMF (1 mL) was added t-butyldimethylsilyl chloride (105 mg, 0.70 mmol). The mixture was heated under a N_2 atmosphere at 35°C overnight whereupon the mixture was diluted with EtOAc and subjected to aqueous washes and extractive work-up in a manner similar to that described for Example 32c giving the title compound (228 mg, 0.49 mmol) as a clear oil which was carried on without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.07 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.47 (s, 9H), 3.67 (dd, J=4.5, 10.5 Hz, 1H), 3.83 (dd, J=4.5, 10.5 Hz, 1H), 4.38 (m, 1H), 4.54 (m, 1H), 4.70 (br s, 1H), 4.99 (br s, 1H), 5.50-5.68 (m, 2H), 7.72 (dd, J=3, 6 Hz, 2H), 7.74 (dd, J=3, 6 Hz, 2H); MS(CI) *m/e* 478 $(m+NH_4)^+$, 461 $(m+H)^+$.

Step 34b. N^2-Methyl-N^2-t-butyloxycarbonyl-2, 5-diamino-1-t-butyldimethylsilyloxy-(2,S)-3,Z-pentene

To the product of example 34a (200 mg, 0.43 mmol) in 1.8 mL anhydrous THF was added CH_3I (0.059 mL, 0.95 mmol) and potassium hydride (35% suspension in oil rinsed twice with hexane, 57 mg, 1.4 mmol). The reaction mixture was allowed to stir under a nitrogen atmosphere overnight. The mixture was diluted with EtOAc and poured into ice-cold aqueous KH_2PO_4. The layers were separated and the aqueous phase was further extracted with fresh EtOAc, then the combined organic extracts were dried over Na_2SO_4 and evaporated to afford 218 mg of the crude product, MS (CI) *m/e* 475 (M + H^+). A 205 mg (0.43 mmol) portion was dissolved in absolute EtOH (4 mL) and treated with N_2H_4 hydrate (0.076 mL, 1.3 mmol). The mixture was stirred overnight at ambient temperature, then at reflux for 2 hr. The mixture was concentrated, diluted with EtOAc, and washed with 5% Na_2CO_3. The aqueous phase was back-extracted with fresh EtOAc, then the combined organic fractions were dried (Na_2SO_4) and conc'd to 160 mg. Chromatography (9:1 $CHCl_3$/MeOH) afforded 66 mg of the title compound. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.05 (s, 6H), 0.88 (s, 9H), 1.46 (s, 9H), 2.78 (s, 3H), 3.41 (m, 2H), 3.50-3.75 (m, 3H), 4.80 (br m, 1H), 5.51 (br m, 1H), 5.81 (br s, 2H). MS(CI) *m/e* 345 $(m+H)^+$.

Example 35

N^4-Methyl-4-amino-1-(N^G-nitroguanidino)-(4,S)-2,Z-penten-5-ol

A solution of Example 34b (63 mg, 0.18 mmol) and TEA (0.028 mL, 0.2 mmol) in MeOH (2 mL) was treated with N-nitro-S-methylthiouronium salt. After stirring for two days, the mixture was diluted with EtOAc and washed twice with 10% aqueous citric acid, once with H_2O, and once with brine, then dried (Na_2SO_4). The mixture was chromatographed (silica gel, 1:1 EtOAc/hexane) to afford 60 mg of purified product. This material was dissolved in 4N HCl/dioxane (5 mL) and stirred for 3 hr, then the solvent was removed and the product was purified by passage through a short pad of silica (CH_3CN/H_2O/HOAc, 12:1:1) to afford product.

Example 36

3-(1,1-Dimethylethyl)-(R)-4-(3-N^G-nitroguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

Step 36a. N-[(1,1-Dimethylethoxy)carbonyl]-S-serine methyl ester

To a solution of L-Boc-serine (0.16 mol) in 150 mL DMF cooled to 0°C and treated with K_2CO_3 (0.16 mol) and MeI (0.32 mol). After 30 min, the reaction was warmed to rt. After 3 hrs, the reaction was partitioned between H_2O and EtOAc, and the EtOAc layer was further washed with brine and dried over $MgSO_4$ to yield 0.15 mol, 93%. R_F 0.5 (EtOAc:hexane 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 3.78 (s, 3H), 3.85-3.98 (m, 2H), 4.36 (bs, H), 5.54 (bd, J=5Hz, 1H); MS(DCI) *m/e* 220 $(m+H)^+$, 237 $(m+NH_4)^+$, 181, 163.

Step 36b. 3-(1,1-Dimethylethyl) 4-methyl-(S)-2,2-dimethyl-3,4-oxazolidinecarboxylate

To a solution of the methyl ester of Example 36a (23 mmol) in 150 mL CH_3CN was added 2,2-dimethoxypropane (2 eq) and p-TsOH (0.1 eq), and the reaction was heated to reflux and gently distilled for 4 hrs. The solvent was evaporated and the residue was mixed with sat. $NaHCO_3$ and extracted with Et_2O. The Et_2O extracts were washed with brine and dried over $MgSO_4$ and concentrated *in vacuo*. Purification was by vacuum distillation at 130°C and 0.4 mm Hg. R_F 0.2 (2:1 hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.42 (s, 5H), 1.50 (s, 5H), 1.53 (s, 2H), 1.63 (s, 1H), 1.67 (s, 2H), 3.77 (s, 3H), 4.02-4.08 (m, 1H), 4.12-4.18 (m, 1H), 4.38 (dd, J=3,7 Hz, 0.6H), 4.99 (dd, J=3.7Hz, 0.4H); MS(DCI) *m/e* 260 ($m+H)^+$, 277 $(m+NH_4)^+$, 221 $(m-C_4H_9)$.

Step 36c. 1,1-Dimethylethyl (S)-4-formyl-2, 2-dimethyl-3-oxazolidinecarboxylate

To a solution of the methyl ester of Example 36b (37 mmol) in 200 mL ϕCH_3 cooled to -78°C was added 1 M DIBAL (65 mmol, in ϕCH_3) over a 15-20 minute

period. The reaction was stirred for 3-4 hr at -78°C and then quenched with CH_3OH (12 mL) at -78°C. The reaction was poured into Rochelle salt (1 M), extracted with EtOAc and the combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product distilled *in vacuo* bp 80-1°C (0.7 mm Hg) as a colorless liquid (80%). R_F 0.45 (1:1 EtOAc:hexane); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.49 (s, 9H), 1.52 (s, 3H), 1.58 (s, 3H), 3.80 (m, 1H), 4.20 (m, 2H), 4.40 (m, 1H), 9.53 (br s, 1H); MS (DCI) 230 $(m+H)^+$, 247 $(m+NH_4)^+$, 191 $(m-C_4H_9)$.

Step 36d. 3-(1,1-Dimethylethyl)-(R)-4-(3-(methoxypropen-2,Z-oyl))-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the aldehyde of Example 36c (28.4 mmol), which was freshly prepared, in THF at rt was added bis-(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl)-phosphonate (1.5 eq) as in example 30d. The reaction was stirred at rt for 4-6 hr and then concentrated *in vacuo*. Purification by flash chromatography eluting with hexane-EtOAc afforded the title compound as a colorless crystalline solid (91%). mp = 52-4°C; R_F 0.6 (1:1 EtOAc:hexane); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.40 (s, 3H), 1.48 (s, 9H), 1.53 (s, 3H), 1.62 (s, 3H), 3.80 (dd, 1H), 4.27 (m, 1H), 5.38 (t, J= 9 Hz, 1H), 5.85 (d, J=10 Hz, 1H), 6.27 (m, 1H); MS(DCI) *m/e* 286 $(m+H)^+$, 303 $(m+NH_4)^+$, 247, 230. Analysis calc'd for $C_{14}H_{23}NO_5 \cdot 0.2\ H_2O$: C 58.20; H 8.16; N 4.85; Found: C 58.35; H 8.11; N 4.78.

Step 36e. 3-(1,1-Dimethylethyl)-(R)-4-(3-hydroxypropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the ester from Example 36d (25 mmol) in anhydrous ϕCH_3 cooled to -78°C was added DIBAL (5 eq) over a 30 minute period. The reaction was stirred at -78°C for 3 hr while following by tlc and then quenched at -78°C with CH_3OH. The product was extracted with EtOAc and the combined organic extracts washed with NaOH, H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography with hexane/EtOAc (1:1) afforded the product as a colorless oil 24 mmol (98%). R_F 0.30 (1:1 EtOAc:hexane); $[\alpha]_D^{20°}$ = +33.5° (c=0.82, CH_2Cl_2) ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 1.49 (s, 3H), 1.56 (s, 3H), 3.70 (dd, 1H), 4.05 (m, 2H), 4.45 (dt, 1H), 4.95 (m, 1H), 5.54 (t, J=9 Hz, 1H), 5.87 (m, 1H); MS(DCI) *m/e* 258 $(m+H)^+$, 275 $(m+NH_4)^+$, 219 $(m-C_4H_9)$.

Step 36f. 3-(1,1-Dimethylethyl)-(R)-4-(3-mesyloxypropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the alcohol from Example 36e (23 mmol) in CH_2Cl_2 at 0°C was added TEA (2 eq) and MsCl (1.5 eq). The reaction was stirred at 0°C for 30 minutes and then extracted with CH_2Cl_2. The combined organic extracts were

washed with cold H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The product was provided in quantatative yield and used directly. R_F 0.65 (1:1 EtOAc:hexane); ^1H NMR (300 MHz, $CDCl_3$) δ: 5.64 - 5.77 (m, 2H), 4.87 - 5.10 (m, 2H), 4.62 - 4.70 (m, 1H), 4.09 (dd, J=7, 8 Hz, 1H), 3.71 (dd, J=3, 8 Hz, 1H), 3.03 (m, 3H), 1.68 (s, 3H), 1.51 (s, 3H), 1.45 (s, 9H); MS(DCI) *m/e* 336 $(m+H)^+$, 353 $(m+NH_4)^+$.

Step 36g. 3-(1,1-Dimethylethyl)-(R)-4-(3-phthalamidopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the mesylate from Example 36f in anhydrous DMF (1.0 M) under a N_2 atmosphere at rt was added potassium phthalimide and the reaction was heated at 80°C for 30 min. The reaction was poured into EtOAc and washed with H_2O, brine and dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The material was purified on silica and eluted with EtOAc/hexane 1/1. The material was a white solid and was obtained in 83%. R_F 0.80, (EtOAc/hexane 5/1); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.48 (s, 9H), 1.55 (s, 3H), 1.61 (s, 3H), 3.70 (dd, 1H), 4.22 (t, J=7.5 Hz, 2H), 4.60 (m, 1H), 5.00 (m, 1H), 5.63 (m, 1H), 7.71 (m, 2H), 7.85 (m, 2H); MS (DCI/NH_3) *m/e* 387 $(m+H)^+$, 404 $(m+NH_4)^+$, 331, 287.

Step 36h. 3-(1,1-Dimethylethyl)-(R)-4-(3-aminopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the phthalimide from Example 36g (0.2 g, 10.9 mmol) in CH_3OH under a N_2 atmosphere was added N_2H_4 (11 mmol) and the reaction mixture was stirred and heated to reflux for 1 hr. The mixture was cooled to rt and poured into EtOAc, washed with H_2O, brine and dried over Na_2SO_4. The product was a slight yellow oil and was obtained in 65.5% yield, 1.82 g (7.1 mmol). R_F 0.80 (EtOAc/PAW 1/1); $[\alpha]_D^{23°}$ = +69.0° (c=0.78, MeOH). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.48 (s, 9H), 1.50 (s, 3H), 1.58 (s, 3H), 3.28 (m, 1H), 3.67 (dd, J=3, 9 Hz, 1H), 4.07 (dd, J=6, 9 Hz, 1H), 4.70 (m, 1H), 5.45 (t, J=12 Hz, 2H), 5.63 (m, 1H); MS (DCI/NH_3) *m/e* 257 $(m+H)^+$.

Step 36i. 3-(1,1-Dimethylethyl)-(R)-4-(3-N^G-nitroguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the amine from Example 36h (513 mg, 2.0 mmol) in EtOH/H_2O (1:1) was added the N-nitro-S-methylthiouronium salt (2 eq) and TEA (1.1 eq). The reaction was stirred at rt for 48 hr and then concentrated *in vacuo*. Purification by flash chromatography eluting with EtOH:H_2O (2:1) afforded the title compound as a white solid (480 mg, 70%). mp = 190°C (decomp); R_F 0.3 (EtOAc-PAW, 1:1); $[\alpha]_D^{23°}$ = +0.90 (c=0.78, MeOH); $[\alpha]_D^{23°}$ = -83.0° (c=1.62,

CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.50 (s, 3H), 1.59 (s, 3H), 3.70 (dd, 1H), 4.05 (m, 1H), 4.10 (m, 1H), 4.40 (m, 1H), 4.64 (m, 1H), 5.50 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 24.5, 27.5, 28.5, 38.3, 54.0, 67.5, 81.3, 93.8, 128.8, 130.5, 152.9, 160.0; MS(DCI) *m/e* 344 $(m+H)^+$, 299, 244 $(m\text{-}Boc+H)^+$; Analysis calc'd for $C_{14}H_{25}N_5O_5$: C 48.97; H 7.34; N 20.40. Found: C 48.74; H 7.72; N 20.22.

Example 37

N^G-Nitroguanidinyl-4(R)-amino-pent-2,Z-ene-5-ol

The protected nitroguanidine from Example 34i was deprotected as in Example 31 to provide the product as a white solid (255 mg, 100%). R_F 0.30 (1:1 EtOAc:PAW); $[\alpha]_D^{23°}$ = -25.1° (c=0.45, H_2O, pH 6.0). ^1H NMR (300 MHz, D_2O) δ: 3.68 - 3.82 (m, 2H), 3.87 - 4.02 (m, 1H), 4.05 - 4.13 (m, 1H), 4.31 - 4.40 (m, 1H), 5.63 (t, 1H), 5.88 - 5.98 (m, 1H); ^{13}C NMR (300 MHz, D_2O) δ: 26.1, 41.2, 52.6, 64.2, 99.2, 127.5, 135.0, 161.7; MS (DCI) 204 $(m+H)^+$. Analysis calc'd for $C_6H_{13}N_5O_3 \cdot 2.4\ HCl \cdot 1.1\ HOAc$: C 27.61; H 5.59; N 19.63. Found: C 27.81; H 5.15; N 19.57. Enantiomeric purity determinations for proucts from Example 31 and Example 37 were performed by chiral HPLC using a Daicel Crownpak CR(+) 4.6x150 mm column and 0.01M perchloric acid mobile phase at 5°C with the results: Example 31, 95.6 % ee; Example 38, 93.6 % ee.

Example 38

N^G-Aminoguanidino-4(S)-amino-pent-2,Z-ene-5-ol

Step 38a. 3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-aminoguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

The product of Example 30h (163 mg, 0.64 mmol) was dissolved in 20 mL Et_2O and treated with TEA (178 µL, 1.28) followed by cyanogen bromide (200 µL, 0.60 mmol, 3M in CH_2Cl_2) added dropwise over 2 min. After 1 hr, the crude reaction mixture was chromatographed on silica gel eluted with 2:1 hexane-EtOAc to provide 150 mg, 0.53 mmol, 83 % yield of the intermediate cyanamide material. The cyanamide (145 mg, 0.52 mmol) was dissolved in 20 mL EtOH and treated with N_2H_4 monohydrochloride (110 mg, 1.7 mmol) at reflux temperature overnight. The reaction mixture was cooled and the residue from solvent evaporation was chromatographed on silica gel and eluted with 20:1:1 CH_3CN-HOAc-H_2O to provide product 147 mg, 0.42 mmol, 70%. R_F 0.4 (5:3 EtOAc-PAW); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 1.50 (s, 3H), 1.57 (s, 3H), 2.00

(s, 3H), 3.70 (dd, J=2, 7 Hz, 2H), 3.78 (bs, 1H), 4.06 (dd, J=6, 8 Hz, 1H), 4.20-4.40 (bs, 1H), 4.56-4.62 (m, 1H), 5.42-5.56 (m, 2H); MS(DCI/NH_3) *m/e* 314(m+H)$^+$, 284, 257.

Step 38b. N^G-Aminoguanidino-4(S)-amino-pent-2,Z-ene-5-ol

The protected product of Example 38a (75 mg, 0.21 mmol) was treated with 1 mL 6N HCl for 3 hr at rt. The crude reaction was diluted with H_2O and lyophilized to provide 58.6 mg, 0.20 mmol, 95% yield (as 5.75 HCl salt); HPLC: 99.1% pure (YMC-ODS-AQ column, elution with H_2O). R_F 0.2 (1:2 EtOAc-PAW); ^1H NMR (300 MHz, D_2O) δ: 3.68-3.81 (m, 2H), 3.99-4.03 (m, 2H), 4.22-4.29 (m, 1H), 5.66 (tt, J=1, 7 Hz, 1H), 5.89-5.97 (m, 1H); MS (DCI/NH_3) 174(m+H)$^+$; $[\alpha]_D^{23°}$ = +9.5° (c=2.1, H_2O); HRMS: Calc'd for: $C_6H_{16}N_5O$: 174.1355; observed: 174.1362. Anal calc'd for $C_6H_{15}N_5O$ • 5.75 HCl: C 18.82; H 5.46; N 18.29; found: C 19.12; H 4.63; N 17.68.

Example 39

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-methylguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the allylic amine from Example 30h in EtOH/H_2O 1/1 (2 mL) was added N,S-dimethyl-pseudothiouronium hydroiodide and TEA and the reaction mixture was stirred at rt for 16 hr. The reaction mixture was concentrated *in vacuo*. The material was purified on silica gel and eluted with 12/1/1 CH_3CN/HOAc/H_2O. The resulting material was a colorless oil and obtained in 81% yield. R_F 0.30 (CH_3CN/HOAc/H_2O 12/1/1); ^1H NMR (300 MHz, CD_3OD) δ: 1.48 (s, 9H), 1.52 (s, 3H), 1.58 (s, 3H), 1.93 (s, 3H), 3.68 (dd, J=9, 12 Hz, 1H), 3.72 (m, 1H), 4.12 (dd, J=9, 12 Hz, 1H), 4.25 (m, 1H), 4.70 (m, 1H), 5.55 (m, 2H); MS(DCI/NH3) *m/e* 313 (m+H)$^+$; $[\alpha]_D^{20°}$ = +80.61° (c=0.962, CH_2Cl_2); Analysis calc'd for $C_{15}H_{28}N_4O_3$ • 2.0 HOAc • 0.9 H_2O: C 50.85, H 8.49, N 12.48; Found: C 50.63; H 8.12; N 12.65.

Example 40

N^G-Methylguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol

To a solution of the protected guanidine of example 39 (1.0 eq) in 66% HOAc (10 mL) was added HCl (2.0 eq) and the reaction mixture was stirred at rt for 1 hr. The solvent was removed *in vacuo*. The material was purified on silica gel and eluted with CH_3CN/HOAC/H_2O 6/1/1. The material was a white solid and obtained in 81%yield. R_F 0.20 (CH_3CN/HOAc/H_2O 6/1/1); ^1H NMR (300 MHz,

D_2O) δ: 2.85 (s, 3H), 3.74 (m, 2H), 4.00 (dd, J=7, 12 Hz, 1H), 4.25 (m, 2H), 5.65 (tt, J=7, 11 Hz, 1H), 5.93 (m, 1H); MS(DCI/NH3) *m/e* 173 ($m+H^+$); $[\alpha]_D^{20°}$ = +18.72° (c=0.561, H_2O); Analysis calc'd for $C_7H_{16}N_4O \cdot 2.9$ HCl: C 30.25, H 6.85, N 20.16; Found C 30.37, H 6.70, N 19.84.

Example 41

3-(N-nitroguanidinoamino-3,Z-butenyl)-2-oxazolidinone

Step 41a. N,N-Di-t-butyloxycarbonyl-3-Hydroxymethyl-6-methyl-[1,6][2,3]-tetrahydropyridazine.

A mixture of 6.95 g (71.0 mmoles) of 2,4-hexadiene-1-ol (Aldrich) and 17.1 g (74 mmoles) of di-tertbutyl-diazo-dicarboxylate (Aldrich) in 25 mL of CH_2Cl_2 was stirred at rt for 20 hr. The mixture was concentrated *in vacuo* to a syrup (24.6 g). A 9.4 g portion of the syrup was purified on silica gel (eluting with 15% EtOAc/hexane to yield a clear thick syrup (9.1 g): R_F 0.41 (20% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 0.5H), 5.72 (m, 0.5H), 5.58 (d, J=10 Hz, 0.5H), 5.49 (d, J=10 Hz, 0.5H), 4.7 (m, 1H), 4.18 (m, 1H), 3.80 (m, 1H), 3.6 (m, 1H), 1.48 (s, 9H), 1.24 (d, J=6.9 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 153.8, 131.8, 130.9, 125.9, 125.0, 81.4, 81.2, 64.5, 62.0, 60.9, 60.0, 28.2, 28.1, 18.5, 18.1; MS(CI) *m/e* 329 $(m+H)^+$.

Step 41b. $N^{2,5}$-Di-t-Butyloxycarbonyl-2,5-diaminohex-3,Z-en-1-ol.

Into a solution of the product of Example 41a (1.54 g, 4.7 mmoles) in 20 mL of THF was distilled 60 mL of NH_3 with vigorous stirring. Sodium metal was added until the solution remained blue, and the reaction mixture was stirred for 90 min, then quenched with anhydrous NH_4Cl. The NH_3 was allowed to evaporate, and the residue was poured into 50 mL of H_2O. The mixture was extracted with 150 mL of 70% EtOAc/hexane. The organic phase was washed with 150 mL of H_2O, then 100 mL of saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$, and concentrated *in vacuo* to give a thick syrup. The syrup was purified by flash chromatography on silica gel, eluting with 50% EtOAc/hexane to yield 125 mg, (8%) of a waxy solid. : R_F 0.36 (50% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (m, 2H), 4.59 (m, 1H), 4.46 (m, 1H), 4.33 (m, 1H), 3.52 (d, J=4.2 Hz, 2H), 1.45 (s, 18H).

Step 41c.3-(t-butyloxycarbonylamino-3,Z-butenyl)-2-oxazolidinone

A mixture of $N^{2,5}$-Di-t-Butyloxycarbonyl-2,5-diaminohex-3,Z-en-1-ol (313 mg) and 23 mg of sodium hydride in 5 mL of THF was stirred at rt for 24 hours, then quenched with 1 mL of EtOH, poured into 100 mL of ether, and washed wtih 100 mL of sat. NaCl. After drying over MgSO4, the

sample was concentrated in vacuo to a thick glass, and purified by chromatography on silica gel, eluting with 40% EtOAc/Hexane to give 172 mg (71%) of product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1 H), 6.98 (s, 1H), 5.42 (t, J = 10 Hz, 1H), 5.18, (t, J = 10 Hz, 1H), 4.88, (m, 1H), 4.44 (t, J = 7 HZ), 4.25 (m, 1H), 3.82, (t, J = 7 Hz, 1H), 1.15 (s, 9H), 1.05 (d, J = 5.5 Hz, 3 H). High Resolution Mass Spectrum caculated for $(m+H)^+$ $C_{12}H_{21}N_2O_4$: 257.1501; found: 257.1507.

Step 41d.3-(amino-3,Z-butenyl)-2-oxazolidinone

165 mg of 3-(t-butyloxycarbonylamino-3,Z-butenyl)-2-oxazolidinone from step 41c was stirred in 3 mL of trifluoracetic acid and 1 mL of H_2O for 30 minutes and concentrated in vacuo. Evaporation from MeOH gave a tan oil 190 mg of the trifluoroacetate salt of 3-(amino-3,Z-butenyl)-2-oxazolidinone. ^{1}H NMR (300 mHz, CD_3OD) δ 5.75 (t, J = 10 Hz, 1H), 5.62 (t, J = 10 Hz, 1H), 4.80 (m, 1H), 4.59 (t, J = 7.5 MHz, 7.5 Hz), 4.27 (m, 1H), 4.02 (m, 1H), 1.35 (d, J = 5.5 Hz, 3H). High resolution mass spectrum calculated for $C_7H_{13}N_2O_2$: 157.0977; found: 157.0971.

Step 41e.3-(N-nitroguanidinoamino-3,Z-butenyl)-2-oxazolidinone

A mixture of 190 mg of 3-(amino-3,Z-butenyl)-2-oxazolidinone from step 41d was dissolved in 2 mL of MeOH with 0.45 mL of TEA, and 95 mg of N-nitro-S-methyl-pseudothiourea was added. After 24 hours, the reaction was concentrated in vacuo to a white paste. The sample was dissolved in 0.5 mL of DMSO, and purified by chromatography on silica gel, eluting with 20% MeOH/EtOAc. The product (R_f 0.46 in the above solvent) was obtained as a white solid following pooling and evaporation of product-containing fractions. The product was dried overnight in vacuo to give 145 mg of a white solid which was recrystallized from MeOH to give 95 mg of a white powder. ^{1}H NMR (500 MHz, DMSO-d6, D_2O) δ 5.41 (m, 2H), 4.80 (m, 1H), 4.51 (t, J = 4.5 Hz, 1H), 4.45 (t, J = 4.8 Hz, 1H), 3.88 (t, J = 4.8 Hz, 1H), 1.10 (d, J = 4.5 Hz, 3 H). High resolution mass spectrum calculated for $(m+H)^+$ $C_8H_{14}N_5O_4$: 244.1046; Found: 244.1042. Combustion analysis caculated for $C_8H_{14}N_5O_4$.(0.13 TEA): C 41.13, H 5.77, N 28.20; Found: C 41.40, H 5.49, N 28.32.

Example 42

2-(N^G-Nitroguanidino)-5-aminohex-3,Z-en-6-ol

The 3-(N-nitroguanidinoamino-3,Z-butenyl)-2-oxazolidinone (71 mg from step 41e) was suspended in 2.5 mL of 8N-HCl and heated at reflux for 48

hours. Removal of solvent under vacuum gave a black glass, which was purified by chromatography on silica gel, eluting with 40:1:1 MeOH/HOAc/H_2O to give 4.2 mg of a clear glass. R_F 0.74, (40:1:1 CH_3OH/H_2O/HOAc); ^1H NMR (300 MHz, D_2O) δ 5.78 (m, 1H), 5.50 (m, 1H), 4.61 (m, 2H), 3.79 (dd, J=4.8, 11.4 Hz, 1H), 3.75 (dd, J=4.8, 11.4 Hz, 1H), 1.31 (d, J=5.7 Hz, 3H); MS (FAB) calc'd for $C_7H_{16}N_5O_3$: *m/e* 218.1253, found: 218.1251.

Example 43

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-benzylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the allylic amine of Example 1h (0.3544g) in EtOH/H_2O 1/1 (6 mL) was added the S-methyl-N-benzylthiouronium salt (1.1eq) and K_2CO_3 (1.1eq) and the reaction was stirred at rt for 24 hr. The reaction was concentrated *in vacuo*. The material was purified on silica gel and eluted with CH_3CN/H_2O/HOAc (12/1/1). The product was a yellow oil and obtained in 61% yield.: R_F 0.50 (CH_3CN/H_2O/HOAc 12/1/1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.49 (s, 3H), 1.58 (s, 3H), 3.72 (dd, J = 4, 11.5 Hz, 1H), 3.85 (m, 2H), 3.87 (d, J = 4.4 Hz, 1H), 4.06 (dd, J= 3, 7.5 Hz, 1H), 5.73 (m, 2H), 6.95 (m, 3H), 7.32 (m, 2H); MS (FAB/MAT90) *m/e* 375 $(m+H)^+$; Analysis calc'd for $C_{20}H_{30}N_4O_3 \cdot 0.25$ H_2O: Calc'd: C 63.38; H 8.11; N 14.78; Found: C 63.26; H 7.90; N 14.87.

Example 44

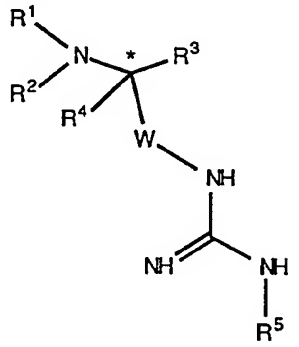
N^G-Benzylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol

To a solution of benzyl guanidine from Example 43 (1 eq.) in CH_2Cl_2 (20mL) was added TFA (3.0 eq) and the reaction was stirred at rt for 1 hr. The reaction mixture was concentrated *in vacuo*. The material was purified on silica gel and eluted with CH_3CN/H_2O/HOAc (3/1/1). The product was a yellow oil and was obtained in 74% yield.: R_F 0.50 (CH_3CN/H_2O/HOAc 3/1/1); ^1H NMR (300 MHz, CD_3OD) δ 3.62 (m, 1H), 3.78 (dd, J=6, 14.5 Hz, 1H), 3.86 (m, 2H), 3.98 (d, J=5 Hz, 1H), 5.80 (dd, J=9, 16.5 Hz, 1H), 5.98 (tt, J=7, 17 Hz, 1H), 7.35 (m, 3H), 7.47 (t, J=9 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 22.1, 43.6, 49.8, 55.6, 63.0, 126.6, 126.9, 128.6, 131.1, 132.4, 157.0; MS (FAB/MAT90) *m/e* 235 $(m+H)^+$; Analysis calc'd for $C_{12}H_{18}N_4O \cdot 3.0$ HOAc: Calc C 52.16, H 7.29, N 13.51; Found: C 51.81, H 7.03, N 13.20.

The foregoing examples are merely illustrative of the invention and are not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which is defined in the appended claims.

What is claimed is:

1. A compound of the formula (I):



(I)

or a pharmaceutically-acceptable salt, ester, amide or prodrug thereof, wherein

* represents a potential chiral center;

R^1 is selected from the group consisting of:

(1) hydrogen;

(2) C_1-C_6-alkyl;

(3) C_6-C_{12}-aryl-C_1-C_4-alkyl;

(4) substituted C_6-C_{12}-aryl-C_1-C_4-alkyl;

(5) N-protecting group;

R^2 is selected from the group consisting of:

(1) hydrogen;

(2) C_1-C_6-alkyl;

(3) C_6-C_{12}-aryl-C_1-C_4-alkyl; and

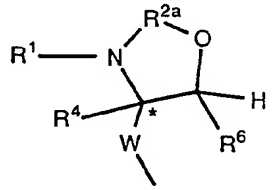
(4) substituted C_6-C_{12}-aryl-C_1-C_4-alkyl;

R^3 is selected from the group consisting of:

(1) CH(OH)-R^6, wherein R^6 is hydrogen, C_1-C_6-alkyl, or C_6-C_{12}-aryl; and

(2) CH(OR^7)-R^6, wherein R^6 is as defined above and R^7 is C_1-C_6-alkyl or a hydroxy-protecting group; or

R^2 and R^3 are linked together by a single bond to form a nitrogen-containing ring of the formula:



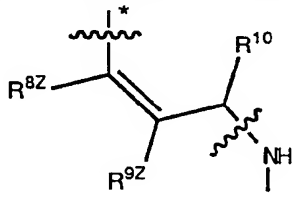
wherein R^1 and R^6 are as defined above, R^4 and W are as defined below, and R^{2a} is $-CR^{13}R^{14}$, wherein R^{13} is selected from the group consisting of:

(1) hydrogen;
(2) C_1-C_6-alkyl;
(3) substituted C_1-C_6-alkyl, as defined below;
(4) C_6-C_{12}-aryl;
(5) substituted C_6-C_{12}-aryl;
(6) C_2-C_6-alkenyl;
(7) carboxy;
(8) C_1-C_4-alkoxycarbonyl, as defined below;
(9) carboxamido; and
(10) cyano; and

R^{14} is hydrogen or C_1-C_6-alkyl;

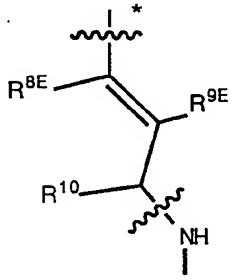
R^4 is hydrogen or C_1-C_4-alkyl;

W is selected from the group consisting of:



(1) ,

wherein the wavy lines identify the bonds which connect to the appropriate atoms of (I), and R^{8Z} is hydrogen or C_1-C_4-alkyl, R^{9Z} is hydrogen, C_1-C_4-alkyl or halogen, and R^{10} is hydrogen or methyl; and



(2) , wherein

R^{8E} is hydrogen or C_1-C_4-alkyl,

R^{9E} is selected from the group consisting of:

(1) hydrogen;
(2) C_1-C_4-alkyl;
(3) C_6-C_{12}-aryl-C_1-C_6-alkyl;
(4) substituted C_6-C_{12}-aryl-C_1-C_6-alkyl;

(5) halo-C_1-C_2-alkyl; and

(6) halogen; and

R^{10} is hydrogen or methyl; and

R^5 is selected from the group consisting of:

(1) hydrogen;

(2) C_1-C_3-alkyl;

(3) cyano;

(4) nitro;

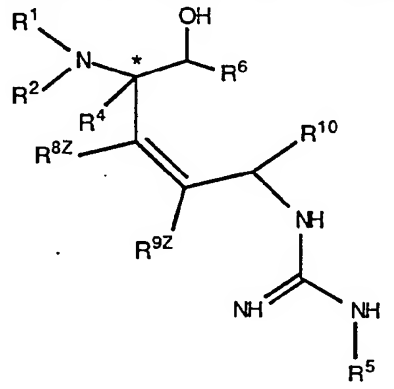
(5) hydroxy;

(6) amino;

(7) $-OR^{11}$, wherein R^{11} is a hydroxy-protecting group; and

(8) $-NHR^{12}$, wherein R^{12} is an N-protecting group.

2. A compound according to Claim 1 represented by formula (Ia):

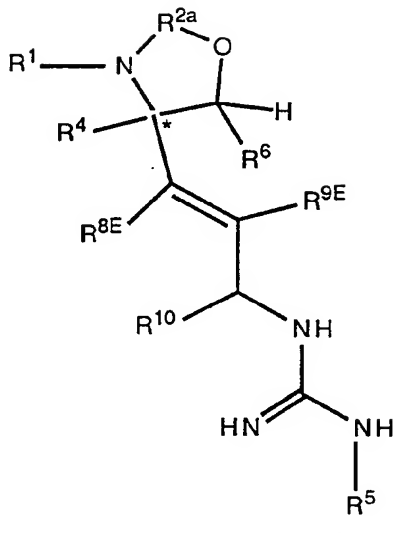


, (1a),

wherein R^1, R^2, R^4, R^5, R^6, R^{8Z}, R^{9Z} and R^{10} are as defined above.

3. A compound according to Claim 2, wherein R^1, R^2, R^4, R^6, R^{8Z}, R^{9Z} and R^{10} are hydrogen and R^5 is nitro.

4. A compound according to Claim 1, represented by the formula (1b):



, (1b),

wherein R^1, R^{2a}, R^4, R^5, R^6, R^{8E}, R^{9E} and R^{10} are as defined above.

5. A compound according to Claim 4, wherein R^5 and R^6 are hydrogen and the chiral center is S.

6. A compound according to Claim 1 selected from the group consisting of:

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-nitroguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Nitroguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

1-Guanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-aminoguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Aminoguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-hydroxyguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Hydroxyguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-methylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-ethylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Ethylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

N^4-Boc-N^G-nitroguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Nitroguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-nitroguanidino-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^4-Boc-N^G-methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(R)-4-(3-N^G-methylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Methylguanidinyl-4(R)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Guanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(R)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

1-Guanidinyl-4(R)-amino-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidino-2-benzyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Guanidinyl-4(S)-amino-2-benzyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-methylguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Methylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-propylguanidino-2-methyl-propen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Propylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-nitroguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Nitroguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol;

N^4-t-Butyloxycarbonyl-4-amino-1-N^G-nitroguanidino-5-methoxy-(4,S)-2,Z-pentene;

4-Amino-1-N^G-nitroguanidino-5-methoxy-(4,S)-2,Z-pentene hydrochloride;

N^2-Methyl-N^2-t-butyloxycarbonyl-2,5-diamino-1-t-butyldimethylsilyloxy-(2,S)-3,Z-pentene;

N^4-Methyl-4-amino-1-(N^G-nitroguanidino)-(4,S)-2,Z-penten-5-ol;

3-(1,1-Dimethylethyl)-(R)-4-(3-N^G-nitroguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;

N^G-Nitroguanidinyl-4(R)-amino-pent-2,Z-ene-5-ol;

N^G-Aminoguanidino-4(S)-amino-pent-2,Z-ene-5-ol;

3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-methylguanidinopropen-1,Z-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;
N^G-Methylguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol;
2-(N^G-Nitroguanidino)-5-aminohex-3,Z-en-6-ol;
2-(N^G-Nitroguanidino)-5-aminohex-3,Z-en-6-ol;
3-(1,1-Dimethylethyl)-(S)-4-(3-N^G-benzylguanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate, or
N^G-Benzylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol.

7. A compound according to Claim 6, which is:

N^G-Nitroguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
3-(1,1-Dimethylethyl)-(S)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;
N^G-Aminoguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
N^G-Methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
N^G-Ethylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
N^G-Nitroguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;
N^G-Methylguanidinyl-4(R)-amino-pent-2,E-ene-5-ol;
N^G-Guanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;
3-(1,1-Dimethylethyl)-(R)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;
N^G-Guanidinyl-4(S)-amino-2-benzyl-pent-2,E-ene-5-ol;
N^G-Methylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;
N^G-Nitroguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol;
4-Amino-1-N^G-nitroguanidino-5-methoxy-(4,S)-2,Z-pentene hydrochloride;
N^4-Methyl-4-amino-1-(N^G-nitroguanidino)-(4,S)-2,Z-penten-5-ol;
N^G-Nitroguanidinyl-4(R)-amino-pent-2,Z-ene-5-ol;
N^G-Aminoguanidino-4(S)-amino-pent-2,Z-ene-5-ol; or
N^G-Methylguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol;

8. A compound according to Claim 7, which is:

3-(1,1-Dimethylethyl)-(S)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;
N^G-Aminoguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
N^G-Methylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;
N^G-Ethylguanidinyl-4(S)-amino-pent-2,E-ene-5-ol;

N^G-Nitroguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;
N^G-Guanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;
3-(1,1-Dimethylethyl)-(R)-4-(3-guanidinopropen-1,E-yl)-2,2-dimethyl-3-oxazolidinecarboxylate;
N^G-Methylguanidinyl-4(S)-amino-2-methyl-pent-2,E-ene-5-ol;
N^G-Nitroguanidinyl-4(S)-amino-pent-2,Z-ene-5-ol; or
N^G-Aminoguanidino-4(S)-amino-pent-2,Z-ene-5-ol.

9. A composition for regulating the production of cyclic guanosine monophosphate comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of Claim 1.

10. A method of treating disorders of the peripheral and cerebral vasculature, the gastrointestinal system, disorders of bronchial smooth muscles, such as asthma, inhibiting blood platelet aggregation during angioplasty, or in the preservation and processing of platelets for transfusions and perfusions, comprising administering to a mammalian host in need of such treatment a therapeutically-effective amount of a compound of Claim 1.

11. A method according to Claim 11 wherein the disorder being treated is hypotension, hypertension, shock, endotoxemia, sepsis, thrombosis, atherosclerosis, migraine, ischemia or non-migraine headache, reflux esophagitis, spasm, diarrhea or irritable bowel syndrome.

INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/US94/04243

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07C 119/00; 129/10
US CL :564/108, 104, 226, 227, 229; 514/634
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/108, 104, 226, 227, 229; 514/634

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,677,226 (LUTZ ET AL) 30 June 1987, column 5, line 50.	1-11
A,P	US, A, 5,296,498 (Malen et al) 22 March 1994, column 1, line 40.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 19 AUGUST 1994	Date of mailing of the international search report 30 AUG 1994
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